



**Trip Report for**  
**“The 237th American Chemical Society National Meeting & Exposition”**  
**Salt Lake City, Utah**  
**March 22-26, 2009**

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**Abstract:** *The 237<sup>th</sup> American Chemical Society National Meeting & Exposition was held in Salt Lake City, Utah from March 22-26, 2009. This National Meeting had attracted over 10,000 chemical scientists from academia and industry. Many interesting papers in the area of medicinal chemistry and organic chemistry were presented. This report highlights select material from the talks presented at the conference.*

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## **“Discovery of S-2367: A potent and selective NPY Y5 antagonist for the treatment of obesity”**

*Takayuki Okuno, et al. Discovery Research Laboratories, Shionogi and Co., Osaka, Japan*

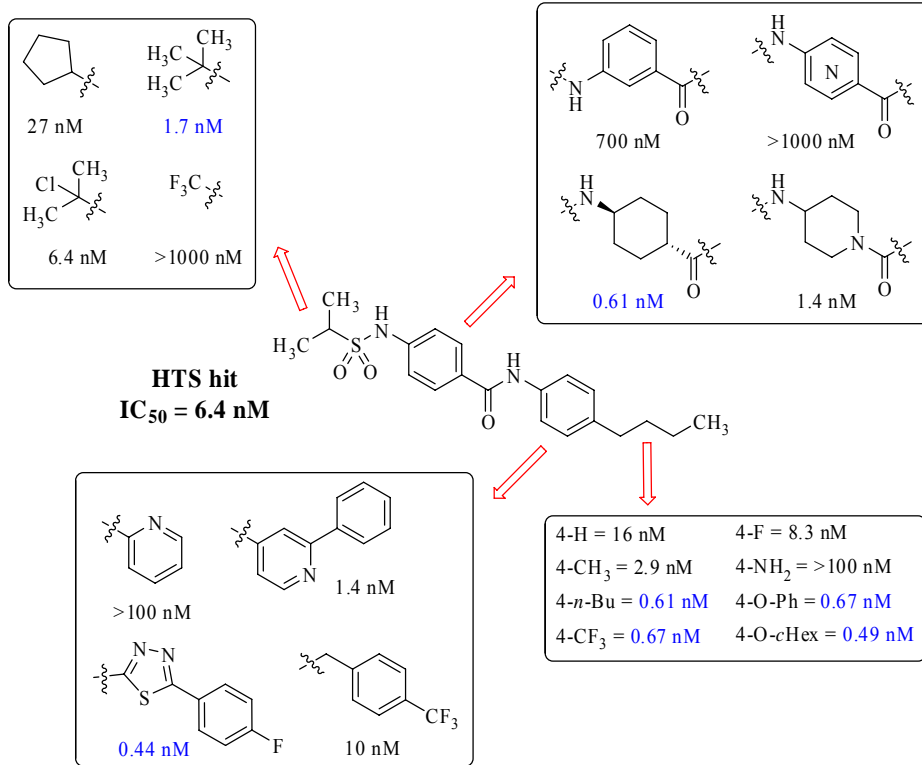
Neuropeptide Y (NPY) is a 36-amino acid peptide neurotransmitter that is widely distributed in the mammalian central peripheral nervous systems. NPY is associated with a number of processes, including the regulation of energy balance, memory and learning, and epilepsy. NPY affects its actions through NPY receptors (Y1, Y2, Y4, Y5, and Y6), which are G-protein coupled receptors. Studies have shown when rats are dosed with NPY, food intake is increased. Alternatively, when Y1 and Y5 receptors were inhibited, NPY actions were blocked and food intake was decreased. Further, it has been shown in obesity models, NPY levels remain persistently high and subtype Y5 is a key receptor in regulating meal initiation and regulation of energy balance. With these studies, Y5 receptor antagonists can potentially serve as anti-obesity therapeutics.

Researchers at Shionogi set up assays in which compounds could be screened for Y1, Y2, Y4, and Y5 binding. Using CHO cells over expressing the NPY receptors, compounds were measured for their ability to displace radio-labeled NPY. To determine if compounds were agonists or antagonists, cyclic AMP accumulation was measured in the CHO cells.

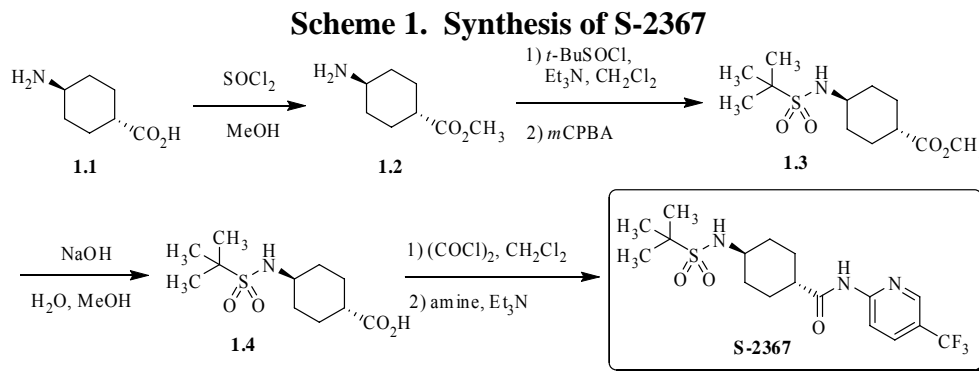
The campaign was initiated with an HTS of the Shionogi compound collection. A family of novel benzanilides was found to be potent antagonists as represented from the compound in Figure 1. A brief summary of the hit-to-lead SAR is depicted in Figure 1. Modification of the sulfonamide portion of the HTS hit resulted in large decreases in activity when the sulfonamide was removed, *N*-alkylated, reversed and homologated. When the alkyl substituent was explored, they found that the *t*-butyl group was optimal. The role of the phenyl group is to spatially arrange the sulfonamide and amide N-H's. The phenyl was replaced by a variety of groups, including 1,3-substituted phenyls, pyridines, pyrimidines, piperidines, bicycles, cyclohexyls, and alkyl chains. Cyclohexyl and piperidine rings were most active. Replacement of the 4-butylphenyl group was also investigated and with the exception of the pyridine ring, a wide range of hydrophobic groups were tolerated at this position. The researchers then explored the substituents on the pendant phenyl ring. Again, it was found hydrophobic groups were preferred and 4-substitution was optimal. Interestingly, large phenyls and cyclohexyl groups showed potent activity.

Based on the SAR for binding and antagonism, the researchers focused on candidate selection using results from *in vivo* PK (bioavailability, total clearance, and brain permeability) and functional *in vivo* models (measurement of food intake). The candidate S-2367 (Scheme 1) did not have the best data in any of the *in vitro* assays, PK studies or the *in vivo* models, however, it did have an optimal overall profile.

**Figure 1. SAR development of the HTS hit**



The synthesis of S-2367 is shown in Scheme 1. Esterification of the *trans*-cyclohexyl amino acid 1.1 gave methyl ester 1.2 which was alkylated followed by oxidation to give sulfoxide 1.3. Saponification of the methyl ester, followed by amide bond formation, gave S-2367.



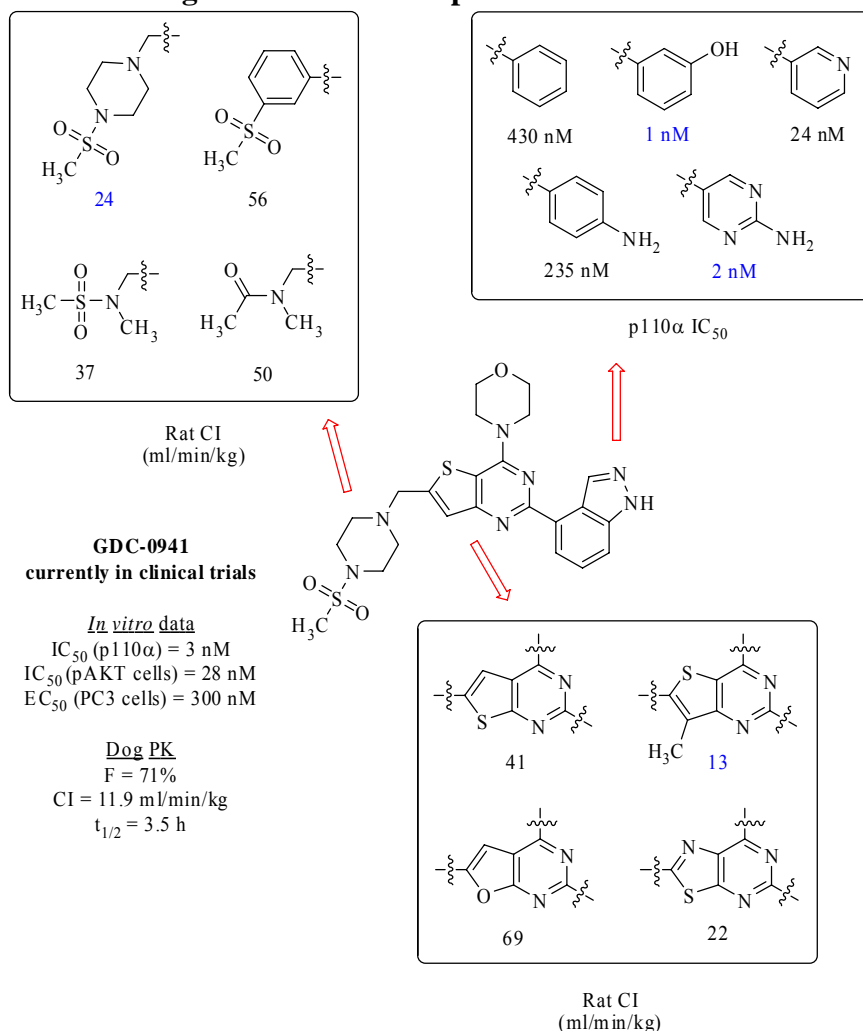
$K_i = 4.8 \text{ nM}$   
 NPY selectivity (vs Y1, Y2, Y4) = >10,000 fold  
 solubility = 1.6  $\mu\text{g/mL}$   
 CYP inhibition, Ames, hERG = clean  
 T 1/2 = 8.6 hr

## “Evolution of a class of potent and efficacious PI3 kinase inhibitors”

Timothy P. Heffron, et al. *Discovery Chemistry, Genentech, Inc., South San Francisco, CA*

Phosphoinositide 3-kinases (PI3Ks) are a family of kinases that phosphorylate the 3-position hydroxyl group on the inositol ring. PI3Ks are divided into 3 classes based on their structure and function. Class I is the only class that can phosphorylate the 3-position of inositol-4,5-diphosphate to inositol-3,4,5-triphosphate (PIP3) on the inner part of the cell membrane. Formation of PIP3 is associated with a wide range of cellular functions, including cell growth, proliferation, differentiation, motility, survival and intracellular trafficking. The class I PI3K subtype p110 $\alpha$  is mutated in many types of cancers: 29% of prostate; 27% of breast; 23% of endometrial; 17% of urinary tract; and 15% of colon cancer. Further, PIP3 phosphatase, PTEN, is absent from these types of cells in which the p110 $\alpha$  subtype is present and therefore, these cells transform into cancer cells.

**Figure 2. SAR development of GDC-0941**

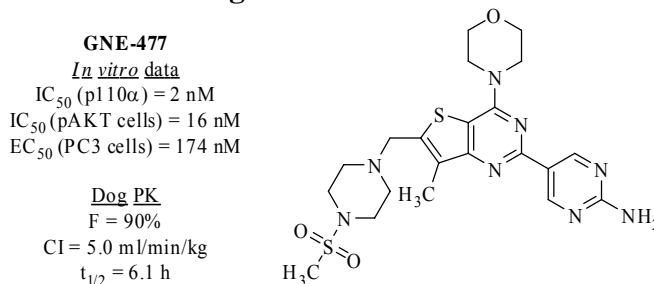


GDC-0941 (Figure 2) is a potent, selective, PI3 kinase inhibitor which is currently being evaluated in human clinical trials by researchers at Genentech. GDC-0941 was identified during a campaign for identification of a clinical candidate for Class I PI3K inhibitors. From the data shown in Figure 2, GDC-0941 has potent activity against the p110 $\alpha$  subtype, potent cell activity, and moderate pharmacokinetic properties. A co-crystal structure with p110 $\alpha$  revealed several key interactions with GDC-0941: the morpholine oxygen can accept a hydrogen bonding interaction with V881 NH; the sulfonamide oxygens, reaching toward the solvent exposed region, can accept a hydrogen bond with K802 on the surface of the kinase; the 1-NH and the 2-N of the indazole motif can interact with the side chain of D841 and Y867, respectively.

As part of this ongoing program, researchers at Genentech aimed to identify additional promising compounds with improved overall ADMET properties. Shown in Figure 2 is part of the SAR development of GDC-0941. On the left side of the molecule, modification of the piperazine-sulfonamide resulted in minimal effects on activity. Some of these modifications did affect the clearance observed in rat but the original piperazine appeared to be the optimal group. Next, the thiophene-pyrimidine core was investigated and the potency was retained by substituting with various bicycles (Figure 2). However based on rat clearance, the methylated thiophene was optimal. At the 2-position of pyrimidine ring, replacement of the indazole with a phenyl group resulted in a large decrease in activity, while a 3-hydroxyphenyl was very potent. Co-crystal structures revealed that the phenol interacted with the same residues as the indazole (D841 and Y867). The pyridyl substitution resulted in a fairly potent compound and the authors speculate that a participating water molecule can induce the same interactions as the phenol. The amino-pyrimidine analogue was potent and a co-crystal structure revealed a new interaction with D836 where the amine appears to interact with both D841 and D836 in a bidentate fashion. The pKa of the amine is favorably modulated by the pyrimidine as evidenced by the poor activity of the simple aniline analogue.

The SAR led to a backup clinical candidate GNE-447 (Figure 3). Although the structures of GDC-0941 and GNE-447 are similar, GNE-447 possesses potent activity against the kinase, more potent activity in cells, better bioavailability, lower clearance, and a new bidentate interaction with p110 $\alpha$  through the amino-pyrimidine motif.

**Figure 3. GNE-477**



## “Discovery of AMG 221: An 11 $\beta$ -HSD1 inhibitor in the clinic for type 2 diabetes”

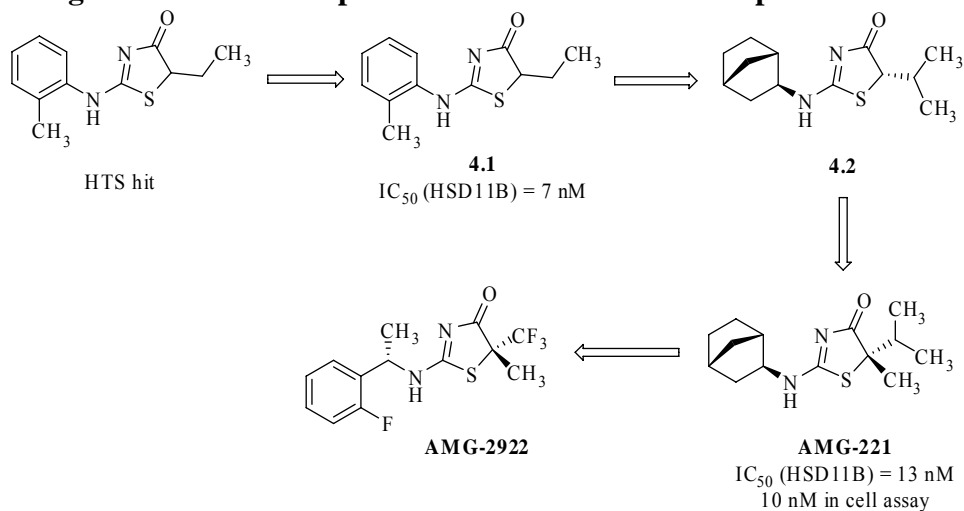
C. Fotsch, et al. Amgen, Inc., Thousand Oaks, CA

11 $\beta$ -Hydroxysteroid dehydrogenase (HSD11B) is a NADPH dependent enzyme which catalyzes the reversible conversion of cortisone to cortisol. The 11-position ketone on ring C of cortisone is reduced to the  $\beta$ -hydroxyl group of cortisol by addition of a hydride. While cortisone is biologically inert, cortisol (also known as hydrocortisone) enters the nucleus of the cell and binds to the GR, which forms a dimer with another GR. This action regulates gene expression and controls the development, homeostasis and metabolism of the organism. Cortisol has many physiological effects, regulating a range of processes from insulin production and immune responses to potassium excretions and memory retention. Pharmacologically, it is used as an anti-inflammatory.

Malfunction in the regulation of cortisol through HSD11B is responsible for many disease states including insulin resistance, hypertension, dyslipidemia, visceral adiposity, and Cushing's disease. Inhibition of HSD11B can regulate the formation of cortisol, favorably affecting lipid profiles and glucose utilization which are key areas for treating metabolic diseases. The indication for HSD11B inhibitors could be used to treat type 2 diabetes.

Researchers at Amgen initiated their HSD11B campaign with a high-throughput screen giving 2-amino-thiazolones as a common core. This HTS hit (Figure 4) was quickly developed to their lead compound 4.1, which showed potent activity against the enzyme. Replacement of the aryl group and investigation of the chirality at the 5-position on the thiazolone led to compound 4.2. This compound was taken into *in vivo* ADMET studies which revealed that epimerization at the 5-position provides an inactive metabolite.

**Figure 4. SAR development of AMG-221 and backup AMG-2922**



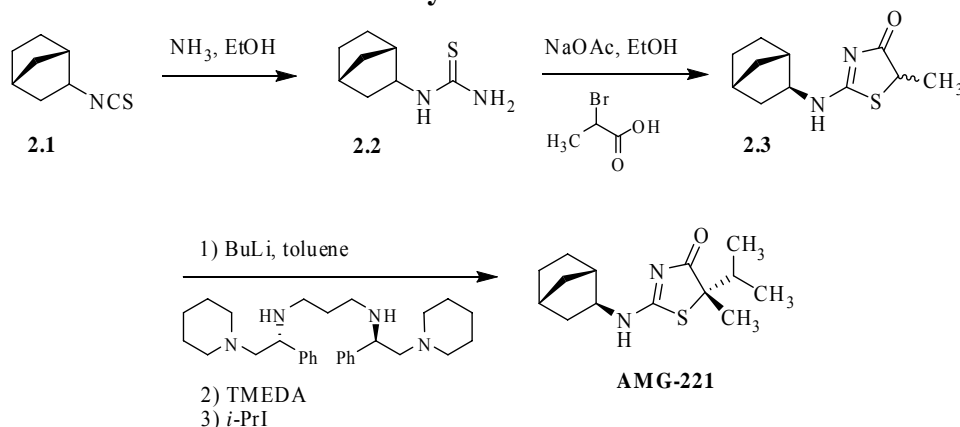
To prevent the epimerization, a methyl group was placed at the 5-position keeping the *S*-configuration of the isopropyl group. Shown in Figure 4 is the clinical candidate AMG-

221, which shows potent enzyme inhibition and cell activity. This compound was taken into the animal efficacy model for type 2 diabetes and showed dose related reduction in insulin production and blood glucose levels. Currently, this compound is undergoing human clinical trials.

Although AMG-221 is a promising clinical candidate, researchers at Amgen began work on a backup candidate. The metabolic profile of AMG-221 revealed particular regions on the molecule that were susceptible to metabolism. The bicycloheptane and isopropyl groups were shown to be soft spots for oxidation. Replacement of the bicyclic and isopropyl groups with a fluorenyl and a trifluoromethyl group, respectively, led to backup candidate AMG-2922 (Figure 4) with much better PK properties.

The large scale synthesis of AMG-221 is detailed in a patent, WO2009002445, from the chemical development department at Amgen. Starting with isothiocyanate 2.1, formation of the thiourea is followed by cyclization to the thiazolone 2.3. Several conditions and chiral inducing agents were investigated for the stereochemical alkylation of the lithium enolate of 2.3. The optimized conditions gave AMG-221 in good yield and high stereoselectivity (>95% de). This route was used to produce AMG-221 in multi-kilogram quantities.

### Scheme 2. Synthesis of AMG-221



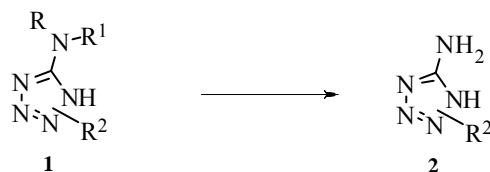

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### “Process for the Preparation of Substituted 5-Aminotetrazoles”

*M. J. Castaldi, T. A. Brandt, S. Lilley, M. R. Shaffer, S. Schuyler, D. C. Whritenour, Pfizer Global Research & Development, Groton, CT*

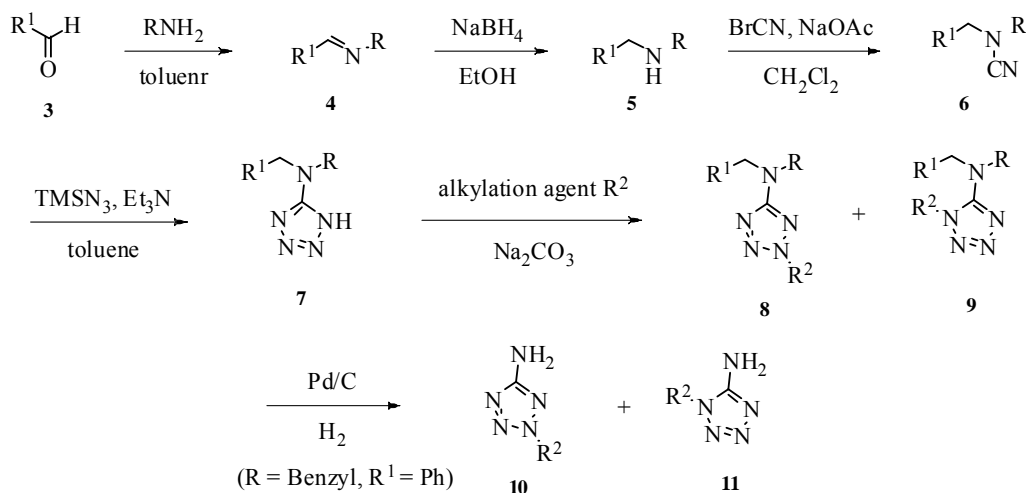
Tetrazoles (**1**) exhibit interesting chemical and biological activity due to spatial and acidic properties which allow them to serve as carboxylic acid bioisosteres and have been a subject of investigation. They have found use in both pharmaceutical and agricultural applications. The literature provides few examples of practical process for the large-scale synthesis of substituted tetrazoles (**1**, Scheme 3).

### Scheme 3



Scientists from Pfizer have developed a scaleable and selective method to prepare substituted tetrazoles (**1**) and subsequently de-protected to afford the 5-aminotetrazoles (**2**) that could be readily incorporated into pharmaceutical agents. The disubstituted amines are available from commercial sources or were synthesized via the appropriate Schiff base. They found that substituted secondary amines were easily converted to amino nitriles using cyanogen bromide in methylene chloride (Scheme 4).

### Scheme 4



The amino nitriles were treated with trimethylsilyl azide and the desired tetrazoles were formed in good yield. They proceeded to alkylate with dimethyl sulfate. The yield of crude alkylated product was excellent and the ratio of regioisomer favored the desired 2-methyl isomer in 90:10 (**8:9**). The two isomers were easily separated via crystallization or could be used crude in the deprotection. This afforded the desired 5-amino-2-methyl tetrazole (**10**, R<sup>2</sup> = Me), and the undesired isomer (**11**, R<sup>2</sup> = Me) which again could be easily separated. A variety of substitution patterns on amino group were explored. They also found that the selectivity for the alkylation at the 2-position increased with the bulk of the alkylation agent.

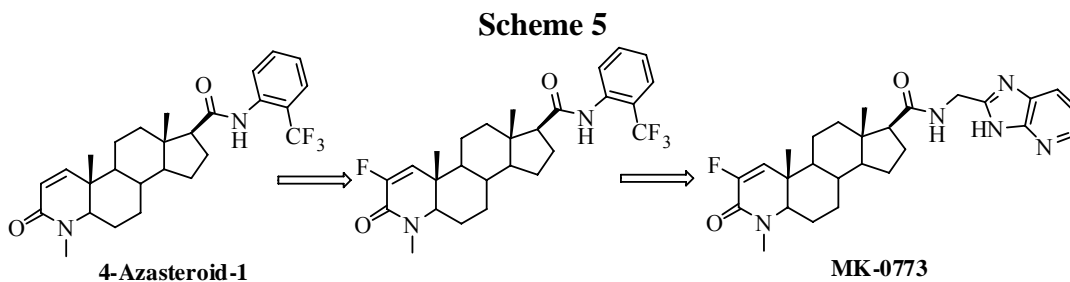
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### “The Discovery and Synthesis of Selective Androgen Receptor Modulator MK-0773”

*J. J. Perkins, C. Bai, F. Chen, M. E. Duggan, L. Freidman, S. Harada, G. D. Hartman, T.-C. Leu, D. B. Kimmel, T. Prueksaritanont, J. Ray, A. Schmidt, and R. S. Meissner, Merck & Co., Inc., West Point, PA*

The Androgen Receptor (AR) is a transcription factor and an important member of the superfamily of nuclear receptors. The AR is found in many tissues, including the prostate, seminal vessel, skin, smooth muscle and bone. The AR is responsible for mediating the physiological actions of the endogenous steroidal androgens testosterone and dihydroxytestosterone (DHT). Several studies have demonstrated that androgens increase bone mass and lean body mass but androgens also have associated adverse effects such as hirsutism in women and prostate growth in men. Tissue Selective Androgen Receptor Modulators (SARMs) are ligands of the androgen receptor that exert AR agonism or antagonism with distinct tissue selectivity providing beneficial anabolic actions on target tissues (bone or muscle) with minimal adverse effects on skin and reproductive tissues. Scientists from Pfizer have developed an orally efficacious SARM, MK-0773 that has anabolic action on muscle and bone with minimal androgenizing effects. MK-0773 has been selected for development and is currently in Phase 2 clinical trials for the treatment of Sarcopenia.

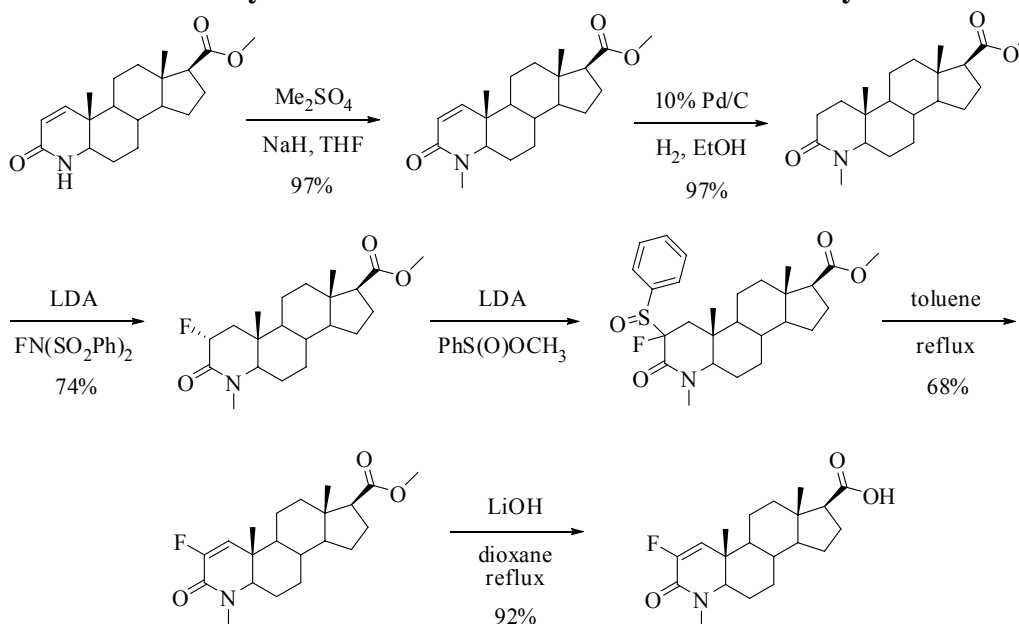
Identified from early medicinal chemistry efforts 4-Azasteroid 1 has demonstrated partial agonism and to increase muscle mass and bone mass with similar efficacy to 0.1 mpk DHT with little adverse effects on skin or uterus tissues in their *in vivo* model assay for sarcopenia and osteoporosis. Starting from 4-Azasteroid 1, they have modified the A-ring and found that the potency was increased by the addition of fluoro substituent at the 2-position (Scheme 5).



They have also replaced the right-hand side aryl amide with an emphasis on increasing the water solubility and improving the oral pharmacokinetic profile. Replacement of the 2-trifluoromethyl aryl amide with the azimidazolyl amide resulted in azimidazole MK-0773. MK-0773 displaced excellent activity and selectivity in the *in vitro* assays and possessed attractive pharmacokinetics parameters in dogs. It was selected for development for the treatment of Sarcopenia.

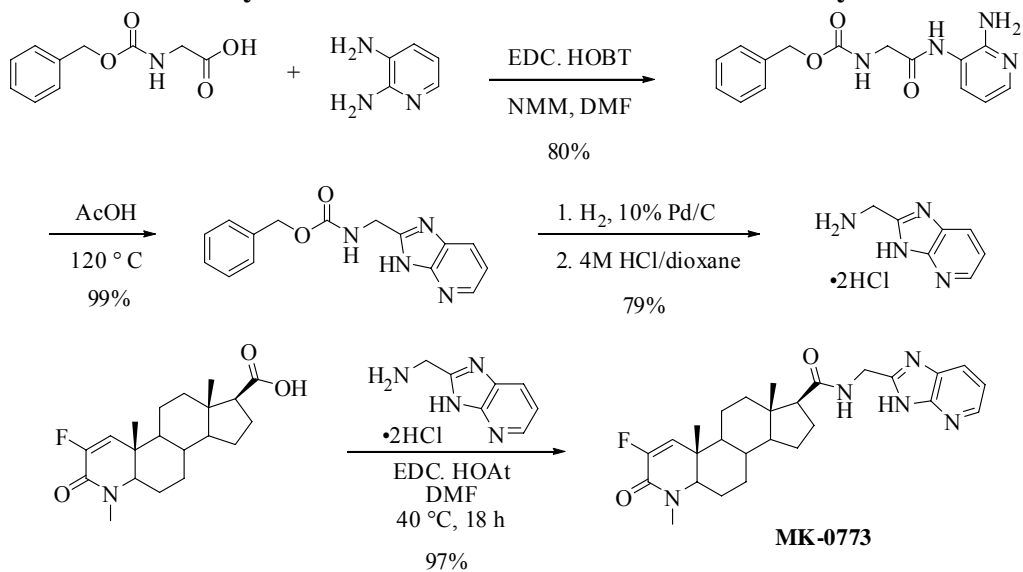
In order to provide the enough material for phase 2 clinical trails, they have developed a novel scalable route to prepare MK-0773. Scheme 6 delineated the synthesis of the left-hand side 2-fluoro-4-azasteroid-17-carboxylic acid.

**Scheme 6. Synthesis of 2-Fluoro-4Azasteroid-17-carboxylic Acid**



The Scheme 7 described the route for preparing the required azaimidazolyl amine and completing the synthesis of MK-0773. They have prepared >150grams via this route.

**Scheme 7. Synthesis of 2-Fluoro-4Azasteroid-17-carboxylic Acid**



**“Inhibitors of Respiratory Syncytial Virus Fusion: Optimization from Screening Leads to Potent, Orally Active Compounds”**

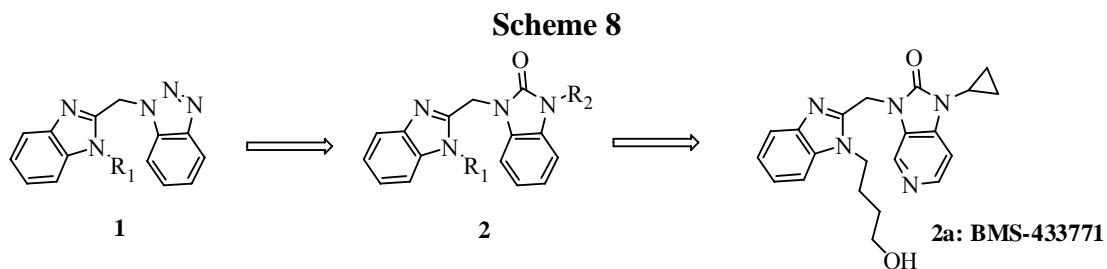
*N. A. Meanwell, Bristol-Myers Squibb Research and Development, Wallingford, CT*

Respiratory syncytial virus (RSV) is a leading cause of respiratory tract infection that infects virtually all children in the first 2 years of life. Although typically restricted to the

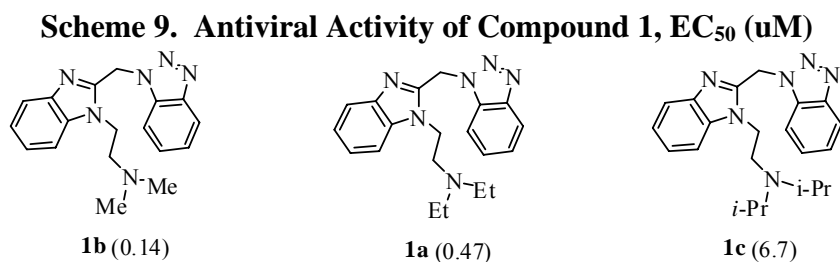
upper respiratory tract, in those who are immunosuppressed or have underlying cardiopulmonary problem, RSV can infect the lower respiratory tract, causing significant morbidity and mortality. RSV is also an underestimated pathogen in the elderly, where it is frequently misdiagnosed as influenza.

Scientists from Bristol-Myers Squibb delineated the discovery of BMS-433771 as potent, selective and orally bioavailable inhibitor of RSV fusion using a tissue cell culture screen. The structure-activity-relationship (SAR) studies that focused on maintaining potency whilst optimizing the balance between metabolic stability and membrane permeability produced compounds with oral bioavailability in animals and antiviral activity in models of RSV infection.

From the initial screening lead they have identified a class of benzimidazole-based inhibitors of RSV fusion **1**, from which evolved a series of more potent RSV inhibitors based on the benzimidazol-2-one template **2** (Scheme 8). This chemotype tolerated a broad range of substituents appended to both the benzimidazole and benzimidazol-2-one moieties that encompassed a wide variation of size and functionality. *In vivo* efficacy towards RSV infection was demonstrated in the cotton rat model with water-soluble derivatives delivered by small particle aerosol. Further optimization for antiviral potency, membrane permeability and metabolic stability in human liver microsomes led to the identification of BMS-433771 (**2a**) as a potent RSV inhibitor with oral bioavailability in mouse, rat, dog and cynomolgus monkey that demonstrated antiviral activity in the BALB/c and cotton rat model of infection following oral administration.

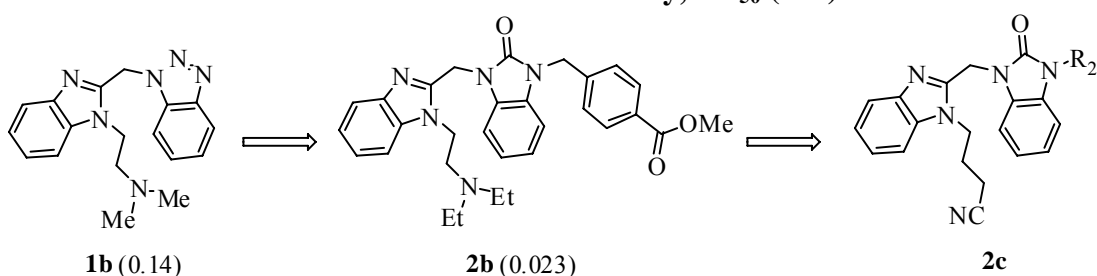


From random screening **1a** was identified. Therefore among others compound **1b** and **1c** were prepared and evaluated for antiviral activity. The SAR exhibited by the homologous series **1b**, **1a** and **1c** indicated a clear preference for less bulky terminal substitution (Scheme 9).



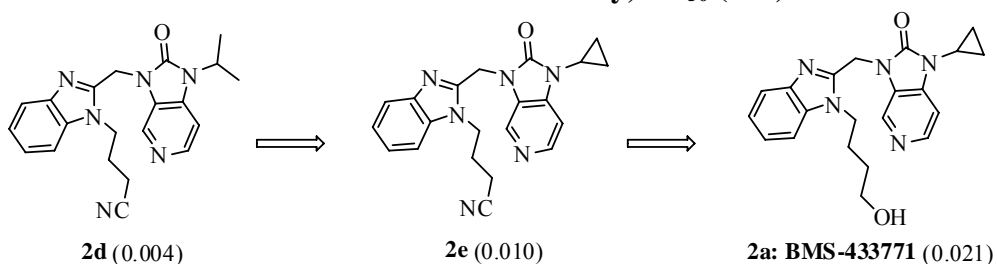
Evolution of benzotriazole chemotype **1b** and further SAR study resulted in the identification of a series of more potent RSV inhibitors based on the benzimidazole-2-one template **2b** (Scheme 10). In order to address the metabolic liability associated with the dimethylaminoethyl side chain of **2b**, the 3-cyanopropyl moiety that conferred potent RSV inhibitory activity in the parent series **2c** was selected for initial studies that were focused on the optimization of the benzimidazol-2-one heterocycle and its *N*-substituent.

**Scheme 10. Antiviral Activity, EC<sub>50</sub> (uM)**



The nitrogen heteroatom was introduced into the benzene element of the benzimidazole-2-one heterocycle with a view to reducing electron density and increasing both the local and overall polarity of the molecule as a means of reducing the rate of metabolism. Since the SAR established earlier indicated that potent antiviral activity can be obtained with the small alkyl (such as *isopropyl*) substituents R<sub>2</sub> attached to the benzimidazole-2-one N atom, this structural theme was also adopted to result in a compound **2d** (Scheme 11). A simple *N-isopropyl* substituent combines excellent antiviral potency and Caco-2 permeability but this compound (**2d**) exhibits poor stability in HLM. The cyclopropyl derivative **2e** offers a unique coalescence of excellent antiviral activity, good *in vitro* metabolic stability and high membrane permeability. These properties appear to be attributable to a combination of the inherent electronic properties of the cyclopropyl ring coupled with a reduction in the overall lipophilicity of **2e** compared to **2d**, which may increase the resistance to metabolic modification.

**Scheme 11. Antiviral Activity, EC<sub>50</sub> (uM)**

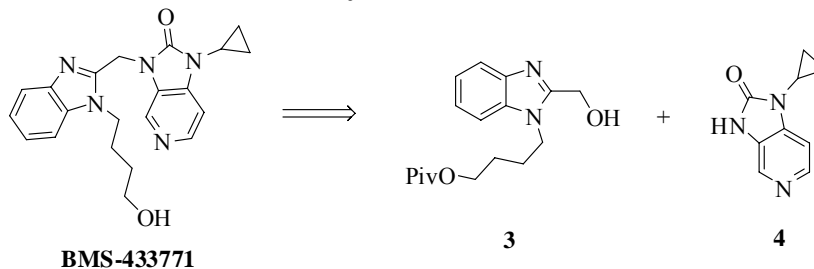


Two compounds, the nitrile **2e** and alcohol **2a**, that meet the target antiviral criterion of EC<sub>50</sub> < 20 nM and combine Caco-2 permeability of greater than 100 nm/s with good metabolic stability, HLM *t*<sub>1/2</sub> of >30 min, were selected for more detailed assessment of pharmacokinetic properties *in vivo*. Both nitrile **2e** and alcohol **2a** were evaluated in toxicological studies with **2a**, designated as BMS-433771, and ultimately selected as a development candidate based on its overall safety profile. BMS-433771 is a selective RSV inhibitor, inactive towards several related and unrelated viruses, that demonstrates

no significant activity towards a broad panel of receptors at a concentration of 10  $\mu\text{M}$ . The compound is not mutagenic in the Ames reverse mutation assay and does not significantly inhibit the major cytochrome P450 isoforms,  $\text{IC}_{50}\text{s} > 26 \mu\text{M}$ , a possible source of concern for pyridine-containing compounds. BMS-433771 is readily accessible at scale and the dihydrochloride salt offers properties sought in a development candidate.

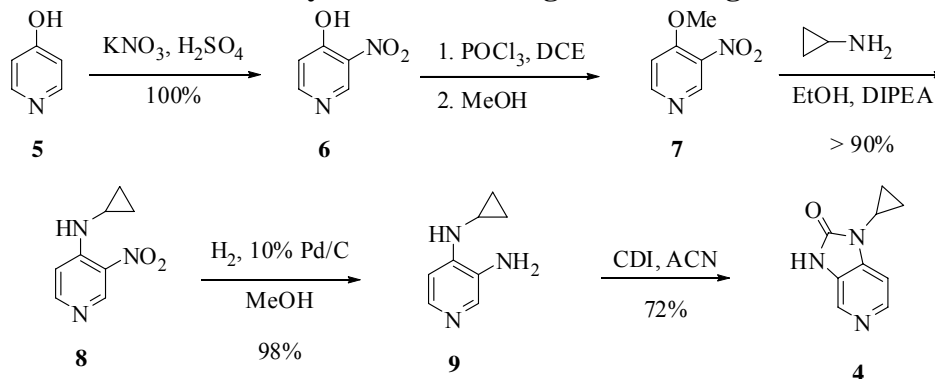
In order to provide a sufficient BMS-433771 for clinical evaluation, BMS scientists have developed a practical route to generate kilogram quantities of material (Scheme 12).

### Scheme 12. Synthesis of BMS-433771



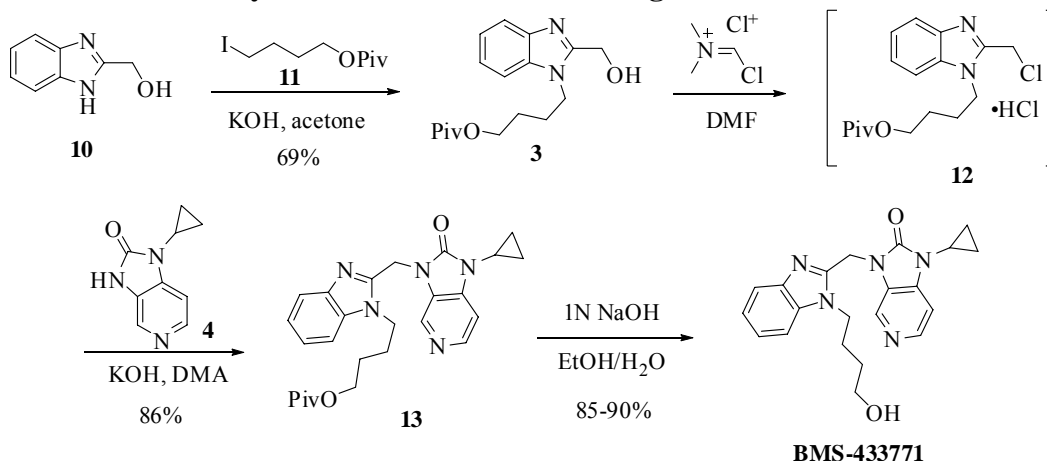
The right-hand fragment **4** was synthesized starting from an inexpensive 4-hydroxypyridine **5** by nitration followed by  $\text{S}_{\text{N}}\text{Ar}$  reaction of **7** with cyclopropylamine to provide cyclopropylaminopyridine **8**. Hydrogenation of **8** followed by cyclization of diamine produced **4** in very good yields (Scheme 13).

### Scheme 13. Synthesis of the Right-hand Fragment 4



The starting material, 2-(hydroxymethyl)benzimidazole **10**, for the right-hand fragment **3** is commercially available or could be synthesized from inexpensive phenylenediamine and glycolic acid. Alkylation of **10** with pivaloyl protected iodide **11** using aqueous KOH in acetone provided **3** in 69% isolated yield (Scheme 14). Vilsmeier-mediated chloride formation followed by coupling with **4** provided the pivaloate protected product **13**. Final deprotection of pivaloate completed the synthesis of BMS-433771.

### Scheme 14. Synthesis of the Left-hand Fragment 3 and BMS-433771

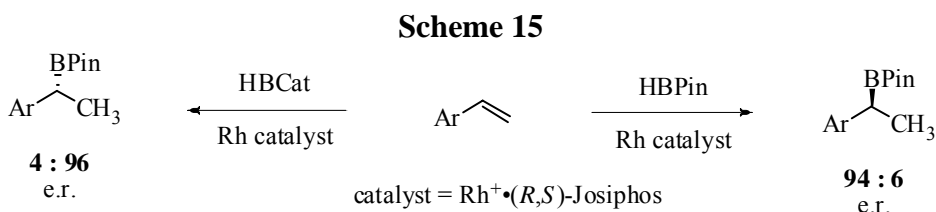


### “Stereoselective Coupling Reactions of Secondary Homochiral Boronate Esters”

*C. M. Crudden, Queen's University, Kingston, ON K7L 3N6, Canada*

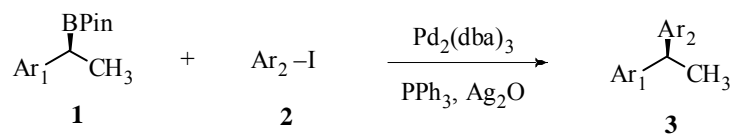
Professor Crudden from Queen's University in Canada described the synthesis of homochiral boronic esters via Rh-catalyzed hydroborations. They have used the Lewis acid additives to improve selectivity and activity. The metal-catalyzed cross coupling reactions using secondary organoboranes are very rare. Crudden and coworkers have devised the first example of the use of chiral secondary organoboronic esters in the Suzuki-Miyaura reaction. Under optimized conditions, this reaction proceeds with virtually complete retention of chirality.

Rhodium metal catalyzed hydroboration of styrenes can be carried out with high levels of regio- and enantio-control (Scheme 15).



Under the optimized conditions, pinacol boronate **1**, prepared by hydroboration of styrene with HBCat followed by a pinacol quench, underwent coupling in good yield, and analysis of the optical purity indicated that >90% of the configuration of the starting material was retained during the coupling reaction (Scheme 16). The reaction tolerates a range of functional groups on either the boronic ester or the aryl iodide (Table 1). They were surprised to find that the reaction is quite specific for secondary organoboronic esters, the corresponding primary boronic esters are not coupled under the same conditions.

**Scheme 16**



**Table 1**

Ar <sub>1</sub>	Ar <sub>2</sub> -I	<b>3</b>	Yield (%)	Stereo-retention (%)
Ph	<i>p</i> -CH <sub>3</sub> COPhI	<b>3a</b>	65	92
Ph	<i>p</i> -ClPhI	<b>3b</b>	81	91
Ph	<i>p</i> -CH <sub>3</sub> PhI	<b>3c</b>	86	92
Ph	3,5-(CH <sub>3</sub> ) <sub>2</sub> PhI	<b>3d</b>	86	93
Ph	<i>p</i> -CH <sub>3</sub> OPhI	<b>3e</b>	48	93
Ph	<i>o</i> -CH <sub>3</sub> PhI	<b>3f</b>	48	93
<i>p</i> -ClPh	PhI	<i>ent</i> - <b>3b</b>	84	84
<i>p</i> -CH <sub>3</sub> Ph	PhI	<i>ent</i> - <b>3c</b>	54	94