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Trip Report for
“The 233rd American Chemical Society National Meeting & Exposition”
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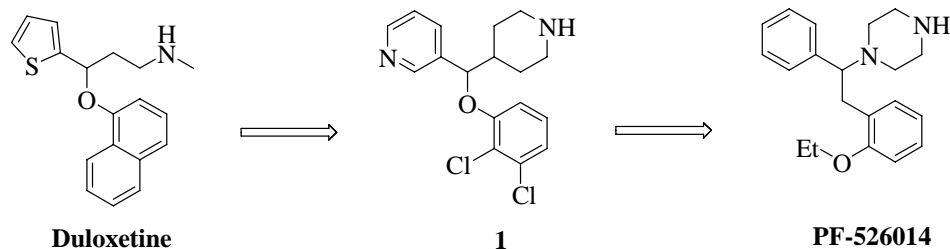
Abstract: *The 233rd American Chemical Society National Meeting & Exposition was held in Chicago, Illinois from March 25 - 29, 2007. The overall theme for this year’s National Meeting was Sustainability of Energy, Food & Water. This National Meeting was well attended by people from academia and industry. 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*

“Discovery of PF-184298, a Dual Serotonin/Noradrenaline Reuptake Inhibitor,”

G. A. Whitlock, F. Wakenhut, A. Stobie, P. V. Fish, M. J. Fray (Pfizer Global Research & Development), Sandwich, United Kingdom.

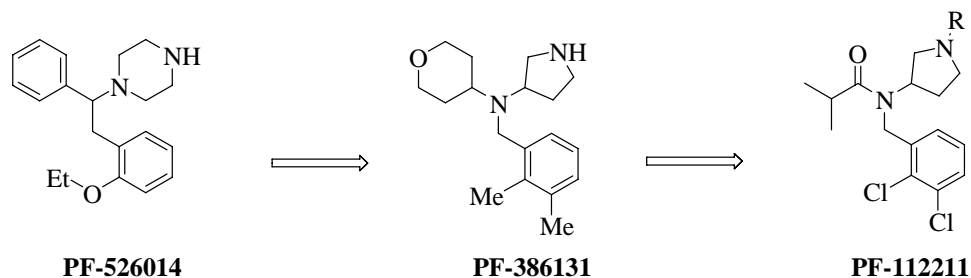
Stress urinary incontinence (SUI) is characterized by the involuntary loss of urine due to a sudden increase in intra-abdominal pressure (e.g. from coughing, sneezing or exercise). Inhibition of serotonin and noradrenaline reuptake (SNRI) has been shown to be an attractive dual pharmacology mechanism for the treatment of SUI. In the presentation Dr. Whitlock highlighted the SNRI medicinal chemistry program at Pfizer including optimization of potency, selectivity, P450 inhibition, CYP2D6 metabolism and pharmacokinetic, which led to the identification of the SNRI clinical development candidate **PR-184298**. Duloxetine, a potent SNRI, is currently under a clinical trial in Europe and likely will be the first to be approved for the treatment of SUI in Europe. The approach taken by Pfizer scientists was to use Duloxetine as a starting point and modify the moieties around the structure of Duloxetine. Their objective for the research project was to find a compound with $K_i < 10$ nM for SRI and K_i ratio 1:3 for SRI/NRI. The compound had to be 100 fold selective over dopamine reuptake inhibition (DRI) and other receptors and ion channels. First they replaced the thiophene ring with pyridine ring and naphthalene ring with 2,3-dichlorophenyl ring. In addition, they tied up the methylaminoethyl side-chain forming a piperidine ring to derive the compound **1** as shown in Scheme 1.

Scheme 1



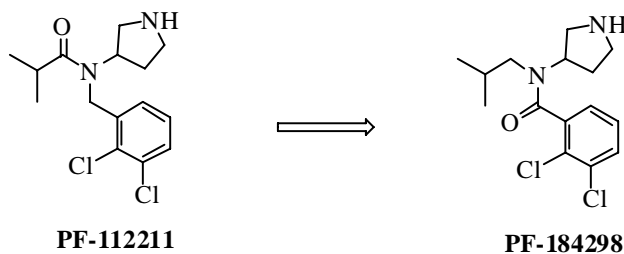
The compound **1** showed good activity, but the selectivity over DRI was poor. The compound **1** was further modified to **PF-526014** by replacing pyridine with phenyl, 2,3-dichlorophenyl with 2-ethoxyphenyl and piperidine with piperazine. They also changed the oxygen linker to carbon. **PF-526014** showed good activity profile (K_i : SERT = 10 nM, NET = 12 nM, DAT > 4000 nM). Unfortunately **PF-526014** exhibited Na and Ca channel off target activities at 400–700 nM. In order to eliminate the ion channels activity they replaced the phenyl ring with tetrahydropyran, 2-ethoxyphenyl with 2,3-dimethylphenyl, and piperazine with pyrrolidine. Three fragments were joined by nitrogen instead of carbon to derive **PF-386131** as shown in Scheme 2.

Scheme 2



Again **PF-386131** showed good activity profile (K_i : SERT = 5 nM, NET = 22 nM, DAT = 570 nM) and no ion channels activity at > 10 μ M. However, this compound exhibited a significant undesired diuretic effect in dog and rat. In order to eliminate the diuretic effect **PF-386131** was further modified to **PF-112211** (R = H). The undesired diuretic effect was eliminated, but no increase in urethral pressure was shown in the dog model. **PF-112211** (R = H) was also found to be a pgp substrate. When R = Me the compound lost its SRI and NRI activities (K_i > 4000 nM) completely. Finally, they switched the amide linkage of **PF-112211** and came up with **PF-184298** as shown in Scheme 3. The activity profile of **PF-184298** is superior to that of Duloxetine. **PF-184298** is currently in a clinical trial for the treatment of stress urinary incontinence. Dr. Whitlock concluded that the small structure alterations can have major effects in the biological activity profile, as demonstrated in their optimization process.

Scheme 3

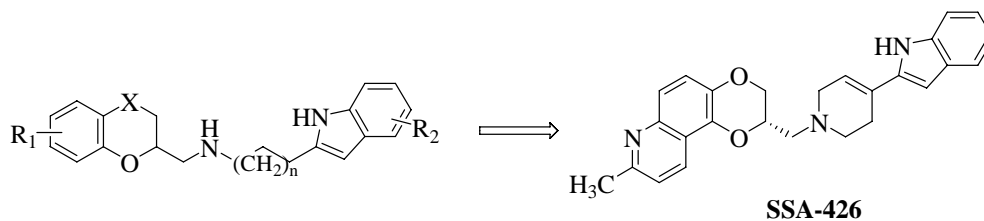


“SSA-426: A Combined SSRI/5-HT_{1A} Antagonist for the Treatment of Depression,”

G. Stack, M. Tran, B. Harrison, J. Gross, G. E. M. Husbands, D. A. Evrard, S. Rosenzweig-Lipson, L. A. Dawson, H. Q. Nguyen, T. Spangler, D. Smith, G. Hornby, R. Scerni, H. Gao, S. Kalgaonkar, G. Zhang, M. Abou-Gharbia, C. Kim, L. Schechter, and T. Andree (Wyeth Research), Princeton, New Jersey.

Dr. Gary Stack from Wyeth Research described the synthesis and structure-activity relationship (SAR) studies leading to the selection of SSA-426 as a development candidate, as well as the biological data predictive of its utility in the treatment of depression. Selective serotonin reuptake inhibitors (SSRIs) represent the current line of treatment for depression. SSRIs, while efficacious in 60–80% of patients, require weeks of treatment before efficacy is observed. This delay in efficacy is believed to be due to activation of inhibitory 5-HT_{1A} autoreceptors, which in time become desensitized. Combining SSRI and 5-HT_{1A} receptor antagonism within one molecule should maximize serotonergic function and result in an immediate increase in synaptic levels of 5-HT. SSA-426 (WAY-163426) is a compound which possesses high affinity for the 5-HT transporter ($K_i = 2.3$ nM) and the 5-HT_{1A} receptor ($K_i = 3.0$ nM). In vitro functional models show that SSA-426 inhibits 5-HT uptake by human 5-HT transporters ($IC_{50} = 145$ nM) and antagonizes agonist-induced stimulation of human 5-HT_{1A} receptors using the functional adenylate cyclase ($IC_{50} = 57$ nM) and GTPγS35 binding ($IC_{50} = 45$ nM) assay. In vivo, SSA-426 produces an immediate and dose-dependent increase in cortical extracellular levels of 5-HT following oral administration to male SD rats, with a MED of 3 mg/kg, p.o. The structure of SSA-426 is delineated as shown in the following Scheme (Scheme 4).

Scheme 4 SSA-426 (WAY-163426)

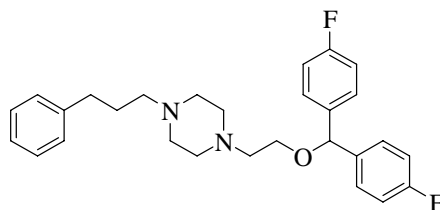


SSA-426 shows good oral bioavailability and no hERG and CYPs activity. The final structure of SSA-426 was derived from linear structure through a series of SAR studies.

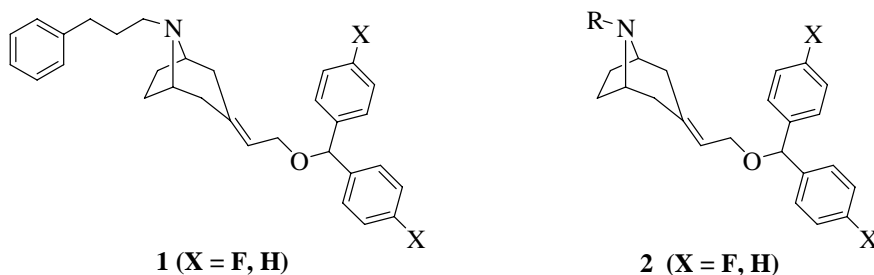
“Synthesis and Biological Activity at Monoamine Transporters of 3-[2-Diarylmethoxy-ethylene)]-N-Substituted Tropane and Azetidine Analogues,”

S. A. Cararas, S. Izenwasser, and M. L. Trudell (University of New Orleans), New Orleans, Louisiana.

The disubstituted piperazine GBR 12909 is a selective high-affinity dopamine transporter ligand and selective dopamine uptake inhibitor. Behavioral studies with GBR 12909 and related derivatives have shown potential for the development of an agonist-based therapeutic agent for cocaine addiction. Although GBR12909 is self-administrated, it has been shown to suppress cocaine self-administration behavior in rhesus monkeys, and exhibit non-stimulant properties in human.



Professor Trudell’s research group from University of New Orleans described the synthesis of a series of 3-[2-(diarylmethoxy-ethylidenyl)]-N-substituted tropane derivatives. The binding affinities of these compounds were determined at the dopamine (DAT), serotonin (SERT), and norepinephrine (NET) transporters in rat brine tissue preparations. A series of potent alkylidene tropane derivatives **1** and **2** were synthesized and evaluated for DAT and SERT binding affinity.



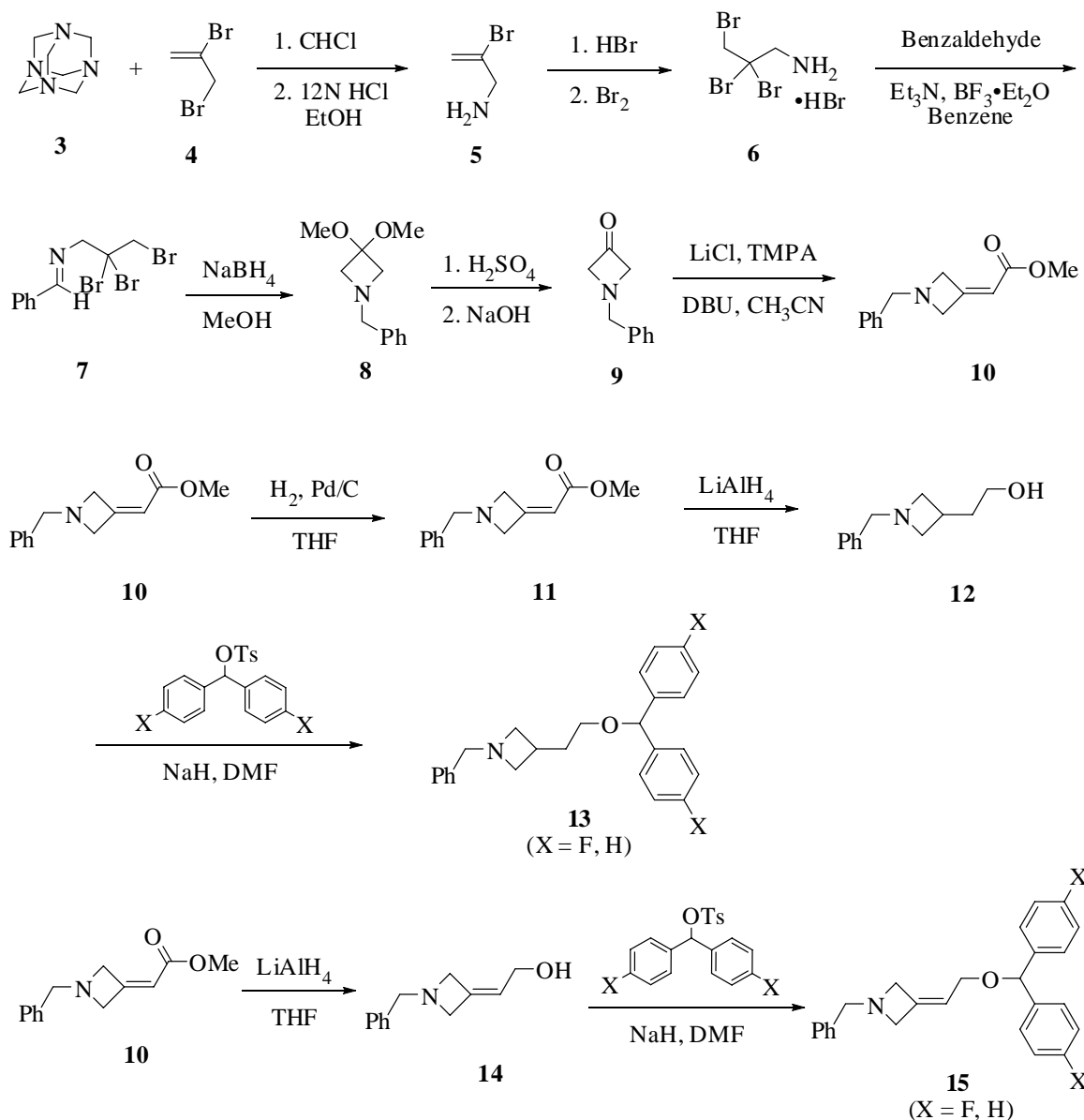
The tropane derivatives **2a** (R = cyclopropyl, X =F) were found to be the most potent ligands ($K_i = 4$ nM) of the series, nearly three-fold more potent than GBR 12909. Furthermore, **2a** (SERT/DAT = 1060) is over 1000 times more selective for the DAT over the SERT compared to GBR 12909.

After successfully replacing the piperazine ring of GBR 12909 with tropane they designed a series of novel azetidine analogues **13** and **15**. They believe that the azetidine

analogues maintain a semi-rigid cyclic skeleton, but being less lipophilic than the tropane analogues. This should improve the bioavailability and faster onset of activity.

The target azetidines **13** and **15** were synthesized from readily available azetidinone **9** (Scheme 5).

Scheme 5
Synthesis of Azetidine Analogues



The SAR studies for azetidine analogues **13** and **15** toward DAT, SERT, and NET transporters affinity are currently under investigation.