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PERSPECTIVE

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Discovery and Development of α7 Nicotinic Acetylcholine Receptor Modulators

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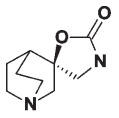
Efforts in the design and discovery of selective α7 nicotinic acetylcholine receptor (nAChR) agonists were both facilitated and hampered by observation that ligands can show dual affinity at both the 5-HT_3 receptor (5-HT_3R) and nAChR.[1] The 5-HT_3R and nAChRs are both part of the Cys-loop superfamily of ligand-gated ion channels. Further, there is significant sequence homology between 5-HT_3R and α7 nAChR in the ligand recognition domain.[2] Previously reported potent α7 nAChR agonists lacked selectivity versus 5-HT_3R,[3] and antagonist activity at 5-HT_3R often translated into agonism at α7 nAChR. The crossover in affinity might be explained by pharmacophoric elements common to both 5-HT_3R and α7 nAChR: a basic amine (protonated at physiological pH) provides for a cation−π interaction; a hydrogen-bond acceptor, e.g., a carbonyl group, forms a hydrogen bond; and aromatic moieties participate in π−π interactions.[4] In view of reported side effects, i.e., constipation, asymptomatic electrocardiogram changes, and arrhythmias, associated with 5-HT_3R antagonists,[5] efforts of research groups were focused on design of ligands specifically interacting with only the α7 nAChR to maximize the therapeutic effect and minimize the adverse effects. Over the past 10 years, drug discovery efforts significantly expanded the quantity and quality of selective α7 nAChR ligands. Those have been summarized in several excellent reviews.[6−8] Despite early skepticism centered around the rapid desensitization of the α7 nAChR and the hypothesis that agonists might not be functional agonists in vivo, 10 of them have already been advanced to clinical trials. In this review, we highlight the most advanced and characterized (especially in vivo) selective α7 nAChR orthosteric and allosteric α7 nAChR modulators.

1. AGONISTS

1.1. Spiroquinuclidines. *(5S)-Spiro[oxazolidine-5,3′-quinuclidin]-2-one (AR-R17779)*[9,10]



1

The conformationally restricted carbamate[19,10] was the first agonist with selective affinity for α7 nAChRs described in the literature: α7 K_i = 92 nM ([^{125}I]α-bungarotoxin binding assay), EC_{50} = 21 μM, E_{max} = 96% at the rat α7 nAChR subtype in oocytes; K_i = 420 nM ([^{3}H]MLA radioligand binding assay), EC_{50} = 420 nM, E_{max} = 93% in human recombinant nAChR subunit combinations expressed in GH4 cells.[11] Despite a less than desirable pharmacokinetic profile[11] and insufficient efficacy, compound **1** served as an invaluable tool for in vivo assessment of α7 nAChR function, validating a link between its activation and a variety of biological effects. Compound **1** has been shown to enhance learning and memory function in rats in a radial arm maze model[12] and social recognition test[13] but has failed to improve performance in a model of attention[14] and had no effect on auditory gating[15] using a prepulse inhibition of the acoustic startle response (relevant to sensory deficits in schizophrenic patients[16]). Compound **1** suppressed the clinical and histologic manifestations of collagen-induced arthritis in mice with established disease, suggesting a link between activation of α7 nAChRs and the inflammatory process in the inflamed joint.[17]

(R)-3′-(3-Methylbenzo[b]thiophen-5-yl)spiro[1-azabicyclo-[2.2.2]octane-3,5′-oxazolidin]-2′-one (W-56203).[20] By modification of the linker between two essential pharmacophoric elements, cationic center (quinuclidine) and aromatic moiety, (+)-3-[2-(benzo[*b*]thiophen-2-yl)-2-oxoethyl]-1-azabicyclo-[2.2.2]octane (**3**) was identified as an α7 nAChR ligand.[18] The aromatic function was modified into (*S*)-3-(benzo[*b*]thiophen-2-ylmethoxy)-1-azabicyclo[2.2.2]octane (**4**). Despite its high affinity (K_i = 13 nM), compound **4** was not detected in plasma following oral administration. The replacement of the metabolically vulnerable oxamethylene spacer between the quinuclidine and benzothiophene in compound **4** with a more rigid carbamate ring was likely inspired by compound **1**. Since compound **5** showed moderate affinity, a library of bicyclic and monocyclic aromatic spiro-carbamates was synthesized. Among monocyclic aromatic derivatives, only compound **6** retained affinity comparable with that of **5**. Optimization of substituents in the thiophene ring led to an enhancement of affinity, producing compound **7** with high oral bioavailability and brain permeability.[19] Unfortunately, it exhibited potent cytochrome P450 2D6 isozyme (CYP 2D6) inhibition, which is considered a liability for potential drug−drug interactions. This prompted reconsideration of the fused bicyclic aromatic spiro-carbamates, which demonstrated reduced CYP 2D6 inhibitory activity. Benzothiophene **8** retained relatively high affinity without inhibition of CYP 2D6 isozyme at 30 μM. Investigation of the effect of a substituent on the ring system provided **2** (Figure 1),[20] which was suitable for in vivo evaluation. Introduction of a methyl group in position 3 of the benzothiophene ring both improved α7 nAChR affinity and diminished the potential to form reactive metabolites through oxidation of the heteroaromatic ring. Compound **2** (Mitsubishi Pharma) improved cognition in auditory sensory gating and reversed the scopolamine-induced impairment of cognitive performance in an eight-arm radial maze task in rat models. Given its

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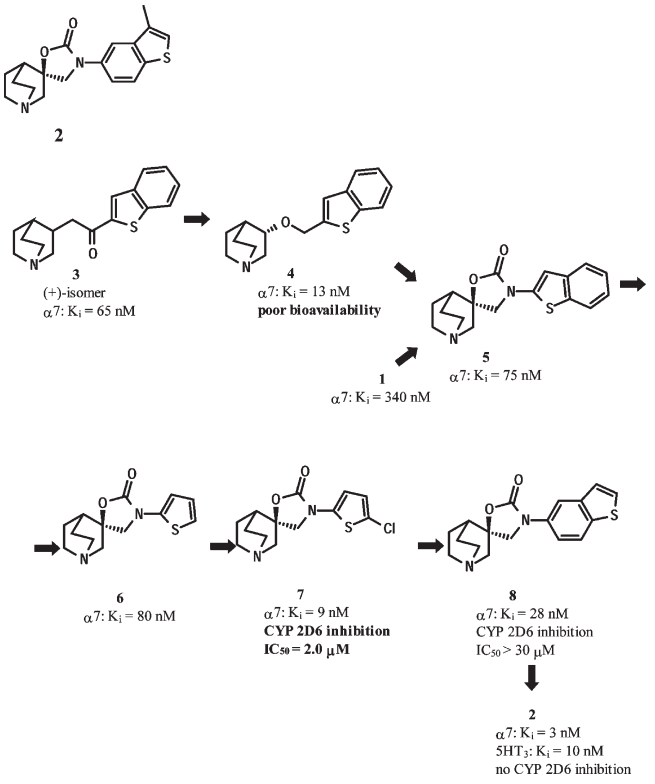


Figure 1. Compound **2**: hit—lead optimization sequence.

moderate pharmacokinetic profile, **2** was reported as a promising drug candidate for the treatment of cognitive impairment associated with neurological disorders. Since this compound significantly increased levels of extracellular dopamine in the medial prefrontal cortex, it was proposed that dopaminergic hypofunction in the prefrontal cortex is responsible for functional abnormalities in schizophrenia.[20]

(2′R)-Spiro-[1-azabicyclo[2.2.2]octane-3,2′(3′H)-furo[2,3-b]pyridine] (AZD0328).[21] Compound **9** (Figure 2) was designed to circumvent the poor pharmacokinetic profile of **1** by replacement of the hydrogen bond acceptor carbonyl moiety with a pyridine nitrogen. 3-Pyridyloxyquinuclidines are known as $5HT_3R$ antagonists,[22] and being a rigid quinuclidinylpyridyl ether, **9** maintained $5HT_3R$ antagonism. Compound **9** improved novel object recognition in mice over a broad range of doses (0.00178−1.78 mg/kg) and working memory (spatial delayed response performance) in rhesus monkeys. The behavioral effects were blocked by pharmacological antagonism of $\alpha7$ nAChR function or genetic deletion of the gene encoding the $\alpha7$ subunit, demonstrating that these actions of **9** are most likely mediated through $\alpha7$ nAChRs. Interaction with $\alpha7$ nAChRs by **9** selectively elevates midbrain dopaminergic neuronal activity, causing an enhancement of cortical dopamine levels; these neurochemical changes might underlie the positive behavioral responses observed in the animal models.[23] Since **9** was unlikely to meet AstraZeneca's target product profile, further development of **9** was discontinued in 2008.[24] Incorporation of aromatic substituents improves interaction with the receptor. Specifically, (2′*R*)-3-(furan-3-yl)spiro-[1-azabicyclo[2.2.2]octane-3,2′(3′*H*)-furo-[2,3-*b*]pyridine][25] (**10**) has the highest affinity (K_i = 0.03 nM) among known $\alpha7$ nAChR ligands. However, the aromatic group facilitates the interaction of the molecule with

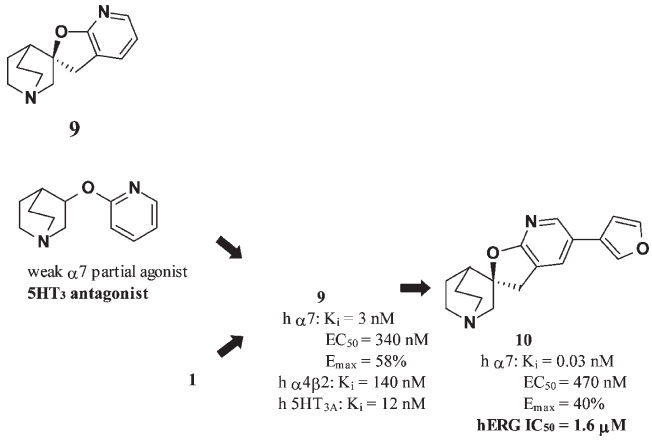
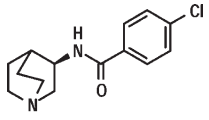


Figure 2. Compound **9**: hit—lead optimization sequence.

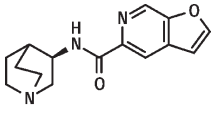
the hERG (human ether-a-go-go-related gene) channel. Optimization resulted in reduction of hERG inhibition by addition of polar substituents. A trade-off of this approach was that the polar substituents converted the series into P-glycoprotein substrates.[26]

1.2. Azabicyclic Arylamides. *N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide (PNU-282987)*[27]



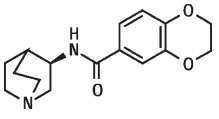
11

N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide (PHA-543613)[28]



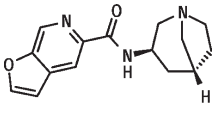
12

N-[3-(R)-1-Azabicyclo[2.2.2]oct-3-yl]-1,4-benzodioxane-6-carboxamide (PHA-568487)[29]



13

N-[(3R,5R)-1-Azabicyclo[3.2.1]oct-3-yl]furo[2,3-c]pyridine-5-carboxamide (PHA-709829)[30]



14

Quinuclidine amides are well explored ligands for nAChR and $5HT_3$ receptors. Amide **15** (Figure 3) was primarily identified

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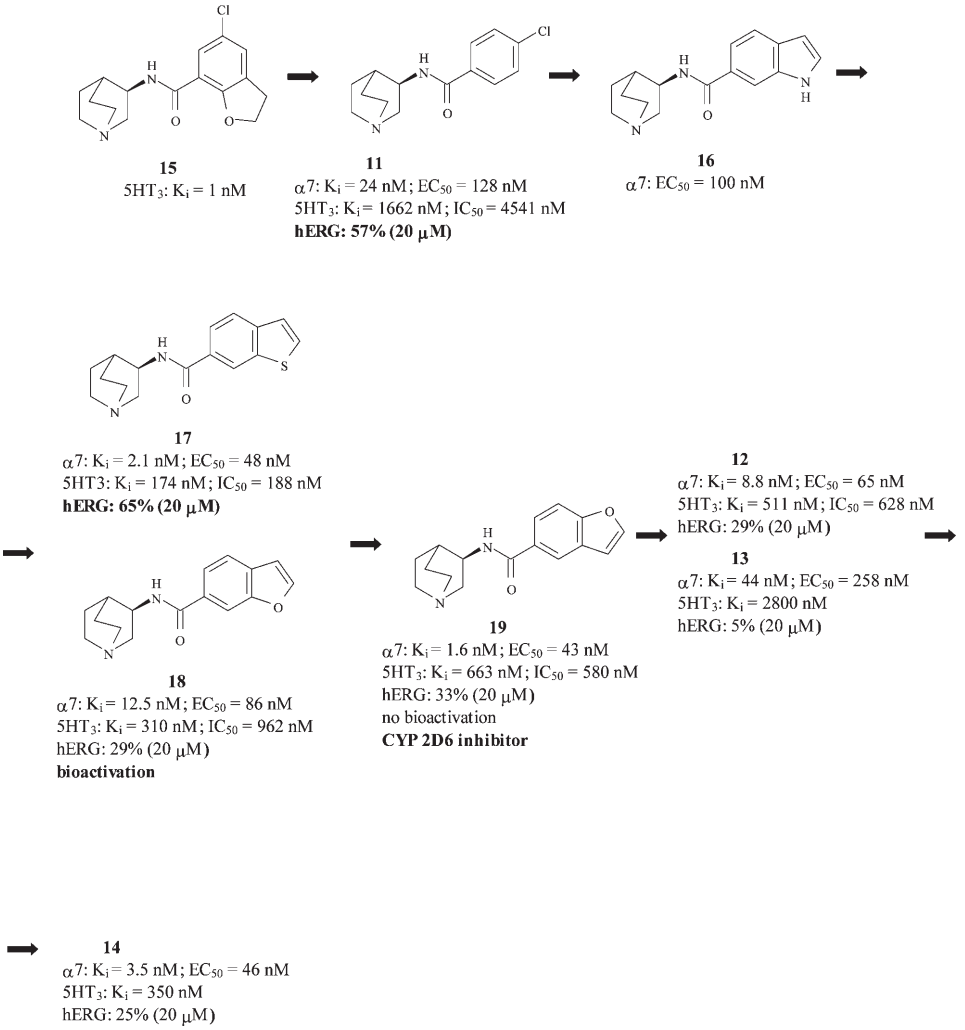

Figure 3. Compounds **16**, **17**, and **18**: hit−lead optimization sequence.

via high-throughput screening as a weak agonist of a chimera of the $\alpha 7$ ($\alpha 7$-5HT$_3$) receptor. Exploration of the substitution pattern around the benzene ring revealed unambiguous SAR for $\alpha 7$ nAChR activity.[27] Ortho-substitution almost eliminates interaction with $\alpha 7$ nAChR, while an *o*-alkoxy group is essential for high affinity to 5HT$_3$R. Compounds with small para-substituents were the most potent $\alpha 7$ nAChR agonists, while meta-substituted benzamides displayed a moderate activity. The $\alpha 7$ nAChR, unlike the 5HT$_3$R, appears to stereospecifically prefer (*R*)-3-aminoquinuclidine aromatic amides for binding. 4-Chlorobenzamide **11** was identified as a potent selective agonist for $\alpha 7$ nAChRs with low affinity to 5HT$_3$R and demonstrated in vivo efficacy in animal models associated with cognitive dysfunction in schizophrenia. However, the compound was not further developed because of significant hERG potassium channel inhibition (11% and 57% at 2 and 20 μM, respectively).[28] Fused heterocyclic analogues, such as indole **16**, preserve $\alpha 7$ nAChR functional potency, providing prospects for improvement of the safety profile. While potent $\alpha 7$ nAChR agonist **17** significantly inhibits the hERG channel, benzofuran **18** was amenable to further optimization. Although an in vitro pharmacological profile of the quinuclidine amide **18** was encouraging, the electron-rich furan ring underwent CYP450-catalyzed oxidative bioactivation, generating reactive metabolites and potential hepatotoxicity. A shift of the electron-withdrawing carboxamide group from position 6 of the benzofuran ring in compound **18** to position 5 in its analogue **19** enhanced affinity and potency and, most importantly, eliminated bioactivation. The last obstacle, inhibition of enzyme CYP 2D6 by benzofuran carboxamide **19**, was circumvented by incorporation of nitrogen into the heterocyclic system. Furopyridine **12** demonstrated efficacy in the reversal of an amphetamine-induced P50 gating deficit and improved performance in a novel object recognition test. Benzodioxane **13**[29] was highly efficacious at 1 mg/kg in the reversal of an amphetamine-induced P50 gating deficit. Both phase I clinical candidates **12** and **13** were discontinued because of cardiovascular findings of nonsustained ventricular tachycardia. Modification of **12** by replacement of (3*R*)-1-azabicyclo[2.2.2]-octane with (3*R*,5*R*)-1-azabicyclo[3.2.1]octane resulted in **14**.[30] The compound is 2-fold more potent than **12** in an amphetamine-induced gating model (MEDs are 0.1 and 0.24 mg/kg, respectively), and it is efficacious over a range of doses (0.1−1.0 mg/kg). In the cardiovascular safety study on dogs, the "no observable adverse effect level" for **14** was established at a dose of 40 mg/kg (C_{max} = 22 μM), which is 5-fold higher than for **12**

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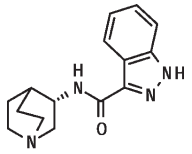
(C_{max} = 3.8 μM). Taken together, the efficacy and safety data represent a 10-fold improvement in cardiovascular therapeutic index for **14** compared to **12**. Additionally, it was shown that **14** remains efficacious after chronic administration.

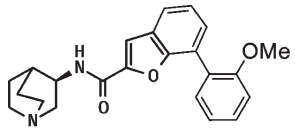
N-[(3S)-1-Azabicyclo[2.2.2]oct-3-yl]-1H-indazole-3-carboxamide (RG3487)[31]



20

Compound **20**[31] (acquired by Roche from Memory Pharmaceuticals and formerly known as MEM3454) displayed high affinity at rat α7 nAChRs with a K_i of 10 nM, as demonstrated by binding to [^{3}H]MLA-labeled sites in rat brain membrane preparation. Assessment of affinity at 5-HT$_3$Rs revealed a slight binding preference for this target, with a K_i of 2 nM. The intrinsic activity profile of **20** (EC_{50} = 0.4 μM, E_{max} = 67%) was determined by whole-cell patch clamp recordings using a cell line stably expressing the monkey wild-type α7 nAChR. Compound **20** displayed minimal affinities/efficacies at other nicotinic receptors ($\alpha4\beta2$, $\alpha3\beta$, and $\alpha1\beta1\delta\gamma$) and showed selectivity against other neurotransmitter and hormone receptor sites in CEREP profiling. Studies using in vitro rat hippocampal CA1 slices demonstrated that **20** (1−10 μM) enhanced 40 Hz long-term potentiation, which was significantly blocked by MLA, thereby demonstrating nicotinic α7 receptor specificity.[32] Compound **20** binds potently to the human α7 nAChR (K_i = 6 nM), in which it acts as a partial agonist (63−69% of acetylcholine) as assessed by whole cell patch-clamp recordings in both oocytes and QM7 cell lines, respectively.[33] Compound **20** activates human α7 nAChRs with EC_{50} of 0.8 μM (oocytes) and 7.7 μM (QM7 cells). Compound **20** also exhibits antagonist properties at the serotonin 3 receptor (5-HT3R; IC_{50} = 2.8 nM [oocytes], 32.7 nM [N1E-115 cells]). Procognitive effects of **20** were demonstrated in behavioral models representing multiple cognitive domains (e.g., episodic, spatial reference, and working memories)[34] with a MED of 1.0 mg/kg po (low-nanomolar range at brain and plasma concentrations) in a novel object recognition test and in models predictive of cognitive and sensory gating restoration in schizophrenia[35] with a MED of 0.03 mg/kg ip in a PPI test and phencyclidine-induced impairment of young and aged rats. Compound **20** showed a significant dose effect on percent hit accuracy performance in rats without any significant alteration on percent correct rejection performance.[36] In a time-dependent test, **20** significantly increased the percent hit accuracy performance when animals were injected 60 min before the start of an attentional task. Administration of galanthamine (acetylcholinesterase inhibitor/α7 nAChR allosteric positive modulator) failed to significantly increase percent hit accuracy performance, and increasing the dose of galanthamine produced a decrease in percent correct rejection performance. In 2007, Memory Pharmaceuticals reported positive results from a phase IIa trial of **20** for the treatment of Alzheimer's disease, but **20** did not reverse cognitive impairment in schizophrenics using the MATRICS scale.[37]

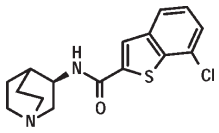
(3R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)-7-(2-methoxyphenyl)-1- benzofuran-2-carboxamide (ABBF)[38]



21

Compound **21**[38] was developed by Bayer Healthcare and showed equal affinity to α7 nAChRs in rat brain membranes (K_i = 62 nM) and to recombinant human 5-HT$_3$Rs (K_i = 60 nM). Compound **21** was a potent agonist at the recombinant rat and human α7 nAChR expressed in *Xenopus* oocytes (EC_{50} of 3 and 5.5 μM, respectively), but it did not show agonist activity at other nAChR subtypes. Compound **21** acted as an antagonist of the 5-HT$_3$R and $\alpha3\beta4$, $\alpha4\beta2$, and muscle nAChRs (at higher concentrations). Compound **21** can improve performance in several learning and memory tests in both rats and mice without producing nicotine-like discriminative stimulus effects. This compound also improved social recognition memory in rats (0.3−1 mg/kg po), and this effect was blocked by intracerebroventricular administration of MLA at 10 μg, indicating that it is mediated by α7 nAChR agonism. In addition, **21** improved working memory of aged rats in a water maze repeated acquisition paradigm (1 mg/kg po) and object recognition memory in mice (0.3−1 mg/kg po).

(3R)-N-(1-Azabicyclo[2.2.2]oct-3-yl)-7-chlorobenzo[b]thiophene-2-carboxamide (EVP-6124)[39]

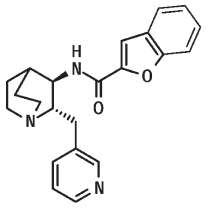


22

In November of 2004, EnVivo Pharmaceuticals licensed from Bayer Healthcare the exclusive rights to its α7 agonist program and identified **22** as a clinical candidate. Compound **22**[39] has been reported to have a favorable brain to plasma exposure ratio and has shown efficacy and potency in a number of animal models of cognition.[40] Compound **22** appears to be well tolerated for up to 21 days as measured by adverse events, vital signs, continuous cardiac monitoring, physical examination, and clinical laboratory evaluations. In addition, in normal volunteers, **22** demonstrated procognitive effects (CogState testing) in various cognitive domains, including executive function. Compound **22** had procognitive effects in two separate clinical trials: one study conducted in Alzheimer's disease patients already treated with acetylcholine esterase inhibitors (AChEI) and one in Alzheimer's disease patients not on AChEI therapy (naive patients).[41] In May of 2011, EnVivo Pharmaceuticals announced positive results of a phase IIb clinical trial of **22** in patients with schizophrenia when taken in combination with second-generation antipsychotics.[42] In clinical trials, the free concentration of **22** in humans administered at daily 1 mg dose was at least an order of magnitude lower than that expected to be required to exert a positive effect on cognitive function or to improve sensory electrophysiological responses that correlate with improved cognitive and functional performance in schizophrenia patients.

This phenomenon was explained by a so-called coagonist effect, which purportedly results in a sensitization of α7 nAChRs. Thus, **22** may produce an environment where smaller amounts of naturally occurring ACh, typically found in individuals with memory disorders such as Alzheimer's, are required to activate the receptor. A phase IIb study of **22** in mild to moderate Alzheimer's disease has also been initiated.

(2S,3R)-N-[2-(Pyridin-3-ylmethyl)-1-azabicyclo[2.2.2]oct-3-yl]-1-benzofuran-2-carboxamide (TC-5619)[44]



23

Quinuclidinylaryl carbamates[47] have been described as one of the first classes of α7 nAChR ligands. Pharmacophore directed diversification around the quinuclidine scaffold through exploration of both positions 2 and 3 (Figure 4) resulted in the discovery of a critical pharmacophoric element in the form of a hydrogen bond acceptor (pyridin-3-yl) in position 2 of the azabicyclic ring.[43] Furthermore, incorporation of a pyridine moiety improved α7 nAChR selectivity by essentially eliminating interaction with $5HT_3$Rs. Further exploration of a hydrogen bond acceptor connecting the cationic pharmacophoric element with the aromatic fragment revealed that a carbamoyl group can be replaced with an amide without loss of affinity, agonism, or selectivity. Optimization of $\pi-\pi$ interaction between the ligand and the receptor resulted in the discovery of **23**.

Compound **23**[44] binds to the α7 nAChR both in rat hippocampal membranes and in a HEK293 cell line coexpressing human α7 and RIC3 cDNAs with a K_i of 1 nM. In a broad receptor selectivity battery (NovaScreen), TC-5619 showed positive interactions in a nonselective opioid receptor assay (58% inhibition) and at the sodium site 2 (79% inhibition). Dose-response assessments of these interactions showed that the K_i values for the opioid site and for the sodium site 2 were both 13 μM, providing a greater than 1000-fold separation from the binding affinity at the α7 nAChR. Binding of **23** (10 μM) to the $5HT_3$R displayed 59% inhibition of radioligand binding at the mouse receptor and 25% inhibition at the human receptor. An investigation of functional activation at the human $5HT_3$R suggested minimal to no activation; a maximal response of 15% was obtained at 100 μM **23**. At human α7 nAChRs transiently expressed in *Xenopus* oocytes, **23** displayed an EC_{50} of 33 nM and an E_{max} of 100% relative to ACh. Compound **23** demonstrated statistically significant enhancement of short-term working memory in the novel object recognition paradigm (MED = 0.3 mg/kg po), and these effects on memory were seen up to 18 h following oral administration, suggesting a positive effect on long-term memory consolidation as well. Compound **23** also reversed apomorphine-induced prepulse inhibition (MED 0.3 mg/kg po) in both mice and rats, which may suggest a benefit against the positive symptoms associated with schizophrenia. The effect of **23** in the social withdrawal model in mice suggests that the compound also has the potential to target negative symptoms of the disease. Taken

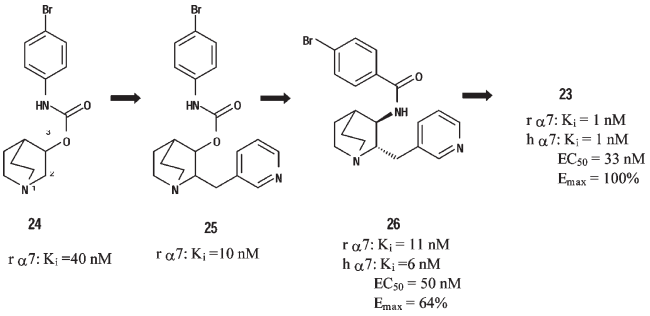


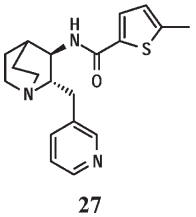
Figure 4. Compound **23**: hit–lead optimization sequence.

together, these findings indicate that **23** may have potential to impact all of the primary domains of schizophrenia, positive symptoms, negative symptoms, and cognitive dysfunction.

Another unique feature of **23** is that its effects appear to be additive or possibly synergistic with those of antipsychotics, further supporting the therapeutic potential of α7 nAChR-selective compounds not only as monotherapy but also together with existing drugs.[44] The transgenic *th(tk−)/th(tk−)*mouse model expresses dopaminergic dysfunction similar to that in schizophrenia and reflects many of the developmental, anatomical, and biochemical aspects of the disease. Although clozapine or 0.1 mg/kg **23** separately had no effect on investigation time, treatment with **23** and clozapine together increased the investigation time of a female stimulus mice in control and homozygous transgenic *th(tk−)/th(tk−)*mice; also, treatment with **23** (0.1 mg/kg) and clozapine together increased the investigation time of a male stimulus animal in *th(tk−)/th(tk−)* but not in control mice.

Compound **23** demonstrated encouraging results on measures of negative symptoms and cognitive dysfunction in schizophrenia and was well tolerated in a phase II clinical proof of concept trial in patients with schizophrenia. Targacept, Inc. reported results from the study at the International Congress on Schizophrenia Research in April 2011.[45] In a separate phase II clinical trial of **23** in adults with attention deficit/hyperactivity disorder (ADHD), conducted in nonsmokers, **23** did not meet the primary efficacy outcome measure. In the study, **23** did demonstrate activity across the various secondary efficacy outcome measures, performing best on the Conners' Adult ADHD Rating Scale—Subject Rated. The product candidate is also in development for Alzheimer's disease.

(2S,3R)-[5-Methyl-N-[2-(pyridin-3-ylmethyl)-1-azabicyclo[2.2.2]-oct-3-yl]thiophene-2-carboxamide (TC-7020)[46]



27

Compound **27**[46] binds to α7 nAChR with high affinity ($K_i \approx$ 2 nM) in displacement studies using [^{3}H]MLA in rat hippocampal synaptosomes and exhibits very poor affinity toward other nicotinic receptor subtypes (K_i > 1000 nM). In functional studies, **27** is an agonist at α7 nAChRs (E_{max} = 69%), as evidenced by voltage-clamp studies of human α7 nAChRs transiently expressed in *Xenopus* oocytes. Compound **27** showed

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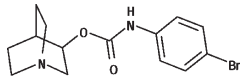
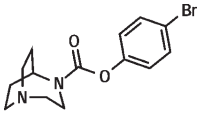
minimal functional activity at muscle (~7% of nicotine's E_{max} at 100 μM) and ganglionic (~6% of nicotine's E_{max} at 100 μM) nAChR subtypes, as shown by measuring calcium flux in TE-671 cells and SH-SY5Y cells, respectively. Compound **27** does not exhibit selectivity for any other (non-nicotinic) receptor targets (IC_{50} > 10 μM), tested at more than 60 targets in a broad receptor selectivity panel. In a model of type 2 diabetes, the homozygous leptin-resistant *db/db* obese mouse, oral administration of **27** reduced weight gain and food intake, reduced elevated glucose and glycated hemoglobin levels, and lowered elevated plasma levels of triglycerides and the proinflammatory cytokine tumor necrosis factor-α.[46] These changes were reversed by the α7-selective antagonist methyllycaconitine, confirming the involvement of α7 nAChRs. Prevention of weight gain, decreased food intake, and normalization of glucose levels were also blocked by the Janus kinase 2 (JAK2) inhibitor α-cyano-(3,4-dihydroxy)-*N*-benzylcinnamide (AG-490), suggesting that these effects involve linkage of α7 nAChR to the JAK2-signal transducer and activator of transcription 3 signaling pathway.[46] The results indicate that α7 nAChRs play a central role in regulating biological parameters associated with diabetes and support the potential of targeting these receptors as a new therapeutic strategy.

1.3. Azabicyclic Carbamates. Aryl carbamates, e.g., **28**, as α7 nAChR ligands were originally reported in 1999.[47] A carbamate oxygen atom is thought to be an essential pharmacophoric element, presumably interacting with α7 nAChR via formation of a hydrogen bond. Consequent exploration of the series by a few research groups resulted in the identification of promising lead compounds with a carbonyl group attached to an endocyclic (**29**) or an exocyclic (**30**) nitrogen.



28
α7 K_i = 167 nM
α7 agonism 90% (32 μM)

(4-Bromophenyl) 1,4-Diazabicyclo[3.2.2]nonane-4-carboxylate (SSR180711)[48]

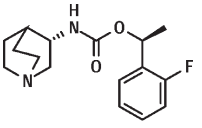


29

Compound **29**[48] displayed high affinity for rat and human α7 nAChRs (K_i of 22 and 14 nM, respectively). In functional studies performed with human α7 nAChRs expressed in *Xenopus* oocytes or GH4C1 cells with ACh as normalizing reference, the compound showed partial agonist effects (intrinsic activity 51% and 36%, EC_{50} of 4.4 and 0.9 μM, respectively). In rat cultured hippocampal neurons, **29** induced large GABA-mediated inhibitory postsynaptic currents and small α-Bgt sensitive currents through the activation of presynaptic and somato-dendritic α7 nAChRs, respectively. In mouse hippocampal slices, the compound increased the amplitude of both glutamatergic (EPSCs) and GABAergic (IPSCs) postsynaptic currents evoked in CA1 pyramidal cells. In rat and mouse hippocampal slices, 0.3 μM **29** increased long-term potentiation (LTP) in the CA1 field. Null mutation of the α7 nAChR gene totally abolished **29**-induced modulation of EPSCs, IPSCs, and LTP in mice. Compound **29** produced a dose- and time-dependent increase in the expression of *Arc* mRNA in the prefrontal cortex and the ventral orbital cortex. The protein *Arc* encoded by the effector immediate early gene *arc* or *arg3.1* has been shown to be strongly implicated in long-term memory function. Thus, α7 nAChR activates a subset of neurons in the rat prefrontal cortex and this activation likely is important for the attentional effects of this new class of drugs.[49]

Compound **29** enhanced episodic memory in the object recognition task in rats and mice and reversed MK-801-induced deficits in retention of episodic memory in rats. It reversed selective attention impaired by neonatal phencyclidine (PCP) treatment and restored MK-801- or PCP-induced memory deficits in the Morris or linear maze. In neurochemical and electrophysiological correlates of antipsychotic drug action, **29** increased extracellular levels of dopamine in the prefrontal cortex and enhanced spontaneous firing of retrosplenial cortex neurons in rats. Compound **29** was proposed to be beneficial not only for the treatment of cognitive symptoms in schizophrenia but also for the positive symptoms as demonstrated in pharmacological and neurodevelopmental latent inhibition models of schizophrenia; the antidepressant-like properties of **29** are of added interest, considering the high prevalence of depressive symptoms in schizophrenic patients. In 2007, Sanofi-Aventis suspended development of **29** for treatment of mild Alzheimer's disease because of an insufficient expected benefit risk ratio.[50]

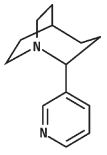
(S)-(1-Azabicyclo[2.2.2]oct-3-yl)carbamic Acid (S)-1-(2-Fluorophenyl)ethyl Ester (JN403)[51]



30

Compound **30** was evaluated by Novartis in a number of in vitro systems of different species, at recombinant receptors using radioligand binding, signal transduction, and electrophysiological studies.[51] When using [^{125}I]α-Bgt as a radioligand, **30** has high affinity for human recombinant α7 nAChR (pK_D = 6.7, K_D = 200 nM). Functionally, **30** is a partial and potent agonist at human α7 nAChR. The compound stimulates calcium influx in GH3 cells recombinantly expressing the human nAChR with a pEC_{50} of 7.0 (EC_{50} 100 nM) and an E_{max} of 85% (compared to the full agonist epibatidine). In *Xenopus* oocytes expressing human α7 nAChR, **30** induces inward currents with a pEC_{50} of 5.7 (EC_{50} = 2 μM) and an E_{max} of 55%. In functional ion-flux assays, **30** shows a 200-fold selectivity over other nAChRs like $\alpha3\beta4$ or $\alpha4\beta2$ as well as $5HT_3$Rs. Similarly, **30** showed low binding activity at a wide panel of neurotransmitter receptors. Compound **30** enhances learning and memory performance in the social recognition test in mice, reverses the auditory gating deficit in anesthetized and awake DBA/2 mice, and is effective in animal models of persistent inflammatory and neuropathic pain.[52]

1.4. Arylazabicycles. *2-(Pyridin-3-yl)-1-azabicyclo[3.2.2]nonane (TC-1698)*[53]



31

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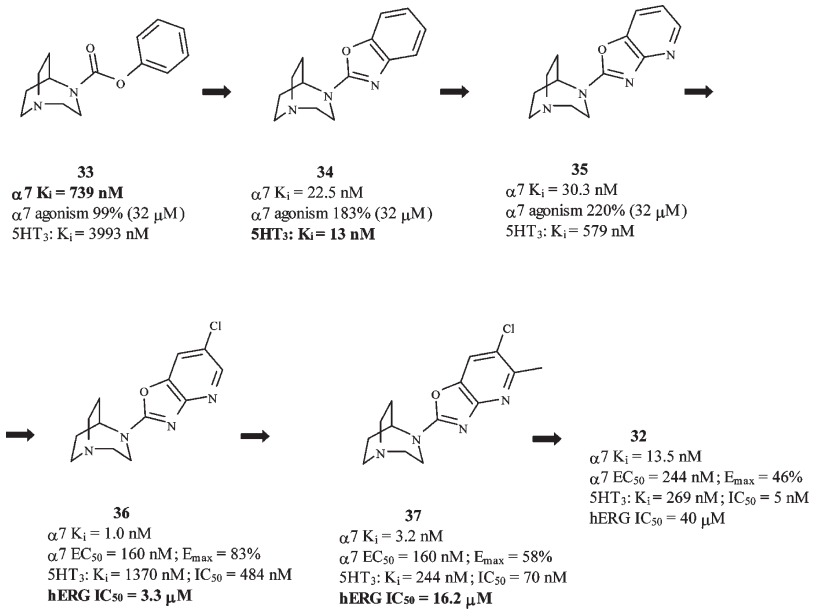
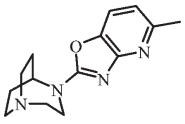


Figure 5. Compound **32**: hit–lead optimization sequence.

Compound **31**[53] is a selective $\alpha 7$ nAChR agonist (EC_{50} = 440 nM, E_{max} = 100%), as determined in human $\alpha 7$ nAChRs transiently expressed in *Xenopus* oocytes using ACh as normalizing reference, with a K_i affinity of 11 nM on membranes prepared from rat hippocampus. A binding profile was conducted to evaluate the interaction of **31** with other receptors, transporters, enzymes, or ion channels. With the exception of nicotinic receptors at which binding was totally displaced, 10 μM **31** had no or very low affinity for all binding sites examined. No (or very low) activation was observed on $\alpha 4\beta 2$, $\alpha 3\beta 2$, $\alpha 3\beta 4$, and $\alpha 1\beta 1\varepsilon\delta$ nAChRs. Compound **31** exerts neuroprotective effects via activation of the JAK2/PI-3K cascade, which can be neutralized through activation of the angiotensin II AT2 receptor. These results support the hypothesis that JAK2 plays a central role in the $\alpha 7$ nAChR induced activation of the JAK2-PI-3K cascade in PC12 cells, which ultimately contribute to nAChR-mediated neuroprotection.

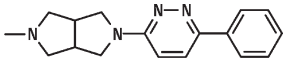
4-(5-Methyloxazolo[4,5-b]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]-nonane (CP-810123)[54]



32

Compound **32**[54] (Figure 5) was discovered by modification of aryl carbamates. Bioisosteric replacement of the carboxy fragment in aryl carbamate **33** with a benzoxazole ring originated a new series of $\alpha 7$ nAChR ligands. Benzoxazole **34** was more efficacious as an $\alpha 7$ nAChR agonist than **33** with ~33-fold improved affinity toward $\alpha 7$ nAChRs. Conversely, such modification had a more drastic impact on $5HT_3R$ binding: $5HT_3R$ K_i was reduced by 307-fold, providing the nonselective ligand **34** for further optimization. Substitutions at the 5- and 6-positions of the benzoxazole ring did not restore the selectivity toward $5HT_3Rs$ to the level of aryl carbamates.[55] As shown earlier in a benzofuran carboxamide series (optimization of compound **12**),[28] replacement of a fused benzene ring with a pyridine ring proved to be a viable option. Among four possible regioisomers resulting in various fusion of an oxazole with a pyridine ring, 4-azabenzoxazole **35** demonstrated potential for improved selectivity over $5HT_3Rs$, maintaining full $\alpha 7$ nAChR agonist activity. SAR exploration of substituted 4-azabenzoxazoles resulted in identification of chloro analogue **36**, which displayed the greatest $\alpha 7$ nAChR affinity and selectivity. Potent hERG inhibition of 6-chloro-4-azabenzoxazole **36** was diminished by addition of a substituent in position 5 of the heterocycle at the expense of selectivity. Nevertheless, compound **37** demonstrated $\alpha 7$ nAChR potency equal to that of **36**, being a $5HT_3R$ antagonist. The authors[54] postulated that the risk associated with $5HT_3R$ antagonism was minimal, since clinical studies suggest that the $5HT_3R$ antagonist ondansetron is well tolerated in patients with schizophrenia.[56] On the basis of evaluation of in vitro potency and selectivity profiles at $\alpha 7$ nAChR, $5HT_3R$, hERG, and genetic toxicity, **32** was selected for evaluation in in vivo efficacy models. It demonstrated efficacy in an amphetamine induced P50 gating deficit model and improved performance in the novel object recognition test. Compound **32** was introduced by Pfizer as a third generation $\alpha 7$ nAChR agonist for treatment of cognitive deficits associated with schizophrenia;[57] to date, there has been no report of its clinical advancement.

3-(6-Phenylpyridazin-3-yl)-7-methyl-3,7-diazabicyclo[3.3.0]-octane (A-582941)[58]



38

While a π–cation interaction has been established as an essential pharmacophore for binding to both $\alpha 4\beta 2$ and $\alpha 7$ nAChRs, the $\alpha 7$ binding site is more lipophilic and presents a less negative electrostatic surface than that for the $\alpha 4\beta 2$ receptor. An elegant approach that converted an $\alpha 4\beta 2$ nAChR agonist into a selective $\alpha 7$ agonist was demonstrated by Abbott's scientists in the case of **38**.[58] A structure–activity relationship study around the highly potent $\alpha 4\beta 2$ nAChR agonist

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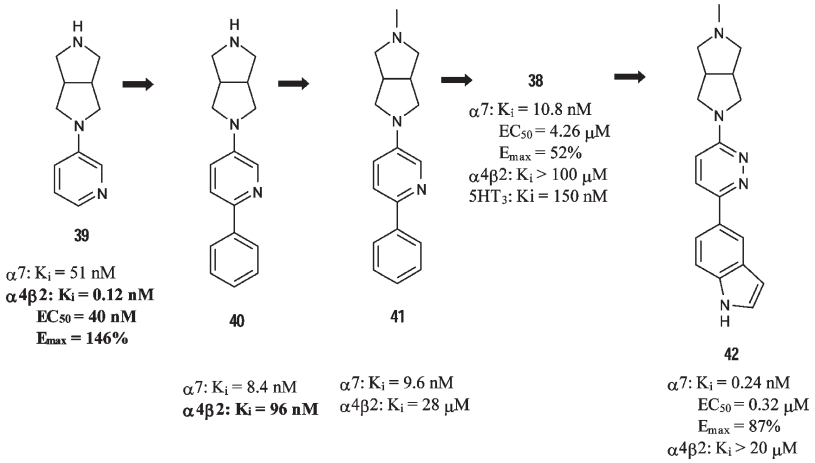

Figure 6. Compound **38**: construction of selective $\alpha 7$ nAChR agonists from an $\alpha 4\beta 2$ nAChR agonist.

3-(pyridine-3-yl)-3,7-diazabicyclo[3.3.0]octane (**39**)[59] revealed that incorporation of a phenyl ring in position 6 of the pyridine resulted in a 6-fold enhancement of potency at the $\alpha 7$ nAChR (Figure 6). Coupled with the decreased affinity for $\alpha 4\beta 2$, compound **40** achieved an 11-fold selectivity for binding to the $\alpha 7$ versus $\alpha 4\beta 2$ nAChR. N-Methylation did not change $\alpha 7$ nAChR affinity while practically eliminating $\alpha 4\beta 2$ binding in compound **41**. Its pyridazine analogue **38** was evaluated further in vitro and in vivo.

Compound **38** exhibited high-affinity binding and partial agonism at $\alpha 7$ nAChRs. Similar affinities were observed in rat brain membranes (K_i = 10.8 nM) and in membranes from human frontal cortex (K_i = 17 nM), indicating that cross-species differences appear to be minimal for this $\alpha 7$ ligand. Compound **38** also displaced the $\alpha 7$-selective antagonist [^{3}H]methyllycaconitine (MLA) from rat brain membranes with a K_i of 88 nM. Compound **38** was screened for activity across a panel of 78 receptor targets including G-protein-coupled receptors, ligand- and voltage-gated ion channels, and neurotransmitter uptake sites. Significant affinity was observed only at the 5HT$_3$R. Compound **38** displaces [^{3}H][(endo-*N*-(9-methyl-9-azabicyclo[3.3.l]non-3-yl-L-methyl-1*H*-indazole-3-carboxamide hydrochloride)] ([^{3}H]BRL-43694) binding to human 5HT$_3$Rs with a K_i of 150 nM, representing approximately 15-fold selectivity for the human $\alpha 7$ nAChR relative to the 5HT$_3$R.

Metabolic conversion of **38** by liver microsomes or hepatocytes in vitro was highly species-dependent, with the rate of turnover fastest in dog, intermediate in rodent and monkey, and slowest in human. Compound **38** exhibits acceptable pharmacokinetic behavior in rodents, dog, and monkey. In mouse and rat, the compound is well absorbed following oral administration, as evidenced by the very high oral bioavailability (100% and 90%, respectively). The much lower bioavailability (22%) in dog is in accord with a much higher rate of metabolism in this species and likely reflects a larger contribution of first-pass metabolism. Consistent with its lipophilic character, **38** is characterized by very large volumes of distribution (4−11 L/kg) and correspondingly high clearance values.

Compound **38** was evaluated across a battery of behavioral assays in rodent and non-human primate models that assess cognitive performance: social recognition in rats, delayed matching-to-sample (DMTS) test in primates, inhibitory avoidance (one trial) in mice, sensory gating in rats and DBA2 mice, and five-trial passive avoidance in spontaneously hypertensive rat (SHR) pups. These studies demonstrate that **38** exhibits broad-spectrum efficacy across various domains of cognition including working memory, short-term recognition memory, long-term memory consolidation, and preattentional sensory gating. With respect to cognitive domains, **38** appears to be especially effective in tasks that involve learning and memory (monkey DMTS at long delay, rat social recognition, and mouse inhibitory avoidance). The procognitive effects of **38** in these models were manifested at similar plasma exposures, approximately 3−6 ng/mL (10− 20 nM) across several models and species. These plasma levels correspond closely to the binding affinity for **38** at the $\alpha 7$ nAChR and are approximately 200-fold lower than the EC_{50} for ion channel opening in vitro, indicating that signaling can occur at agonist concentrations well below those required for a macroscopic current in oocytes, measured as the synchronous opening of many channels elicited by rapid application of agonist. It was suggested that low concentrations of agonist can elicit a small but sustained current by stimulating the opening of a small percentage of the $\alpha 7$ nAChR. Individual receptors may be stimulated, desensitized, and recovered with normal dynamics, while the size of the pool of open channels remains relatively stable at any one time.

Secondary pharmacodynamic and tolerability profiles of **38**[58] were assessed in a battery of assays of cardiovascular, gastrointestinal, and CNS function. In animal experiments, **38** was well tolerated at exposures greater than those required for efficacy in cognition models. In rats, single oral dosages of 400 mg/kg (1400 μmol/kg) induced clinical signs indicating CNS activity, such as tremor and spasms. A dose of 800 mg/kg, po, was lethal within 10 min. To explore the potential of **38** to promote tumor growth, the compound was applied to shaved skin patches on the backs of SENCAR (sensitive to carcinogens) mice every 2 days for a period of 2 weeks. Compound **38** produced only a mild irritation of the skin, with no histologic evidence of epidermal hyperplasia or increased proliferation of basal keratinocytes as assessed by immunohistochemical detection of bromodeoxyuridine reagent.

Comprehensive detailed characterization of **38** in combination with its broad-spectrum efficacy, favorable tolerability, and relatively low potential for toxicity has made it a valuable tool compound for evaluation of the $\alpha 7$ nAChR platform and as a candidate for potential drug development.

Exploration of substitution in the phenyl ring of **38** and the observation that a hydrogen bond donor in the para-position of

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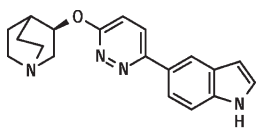
the phenyl ring enhanced α7 binding resulted in replacement of the terminal phenyl by an indolyl group to obtain the most potent α7 ligand (**42**) identified in the series.

5-(6-[(3R)-1-Azabicyclo[2,2,2]oct-3-yloxy]pyridazin-3-yl)-1H-indole (ABT-107)[60]



43

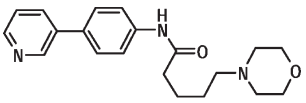
Clinical drug candidate **43**[60,61] was introduced to address the potential issues that are likely to be encountered in the clinical development of an α7 nAChR agonist for the treatment of Alzheimer's disease. Those issues may include drug−drug interactions in patients already receiving other AD therapeutics, dosing constraints defined by pharmacokinetic−pharmacodynamic (PK−PD) limitations, and adverse events, in particular, nicotine-like abuse liability.

Compound **43** is structurally related to **42** containing the same hydrophobic aromatic moiety, (indol-5-yl)pyridazin-6-yl, and common for α7 agonists quinuclidine, as a cationic pharmacophoric element. Compound **43** displayed high affinity binding to α7 nAChRs [rat or human cortex, [^{3}H](1*S*,4*S*)-2,2-dimethyl-5-(6-phenylpyridazin-3-yl)-5-aza-2-azoniabicyclo[2.2.1]heptane (A-585539, **57**),[62] K_i = 0.2−0.6 nM, or [^{3}H]MLA, 7 nM] that was at least 100-fold selective versus non-α7 nAChRs and other receptors. Functionally, **43** did not evoke detectible currents in *Xenopus* oocytes expressing human or non-human α3β4, chimeric (α6/α3)β4, or 5-HT$_{3A}$ receptors, and weak or negligible Ca^{2+} responses in human neuroblastoma IMR-32 cells (α3* function) and human α4β2 and α4β4 nAChRs expressed in human embryonic kidney 293 cells. Compound **43** potently evoked human and rat α7 nAChR current responses in oocytes (EC_{50} of 50−90 nM total charge, ∼80% normalized to acetylcholine) and enhanced spontaneous inhibitory postsynaptic current activity in dentate gyrus granule cells. Both effects were augmented by the positive allosteric modulator 4-[5-(4-chlorophenyl)-2-methyl-3-propionylpyrrol-1-yl]benzenesulfonamide (A-867744). In rat hippocampus, **43** evoked α7-like currents in rat hippocampus, which were inhibited by the α7 antagonist MLA. In the presence of **11**, the addition of **43** elicited MLA-sensitive α7 nAChR mediated Ca^{2+} signals in IMR-32 cells and rat cortical cultures and enhanced extracellular signal-regulated kinase phosphorylation in differentiated PC-12 cells. Compound **43** was also effective in protecting rat cortical cultures against glutamate-induced toxicity.

In in vivo experiments,[61] **43** improved cognition in monkey delayed matching to sample, rat social recognition, and mouse two-trial inhibitory avoidance and continued to improve cognitive performance at times when exposure levels continued to decline. Rats concurrently infused with **43** and donepezil at steady-state levels consistent with clinical exposure showed improved short-term recognition memory. Compared with nicotine, **43** did not produce behavioral sensitization in rats or exhibit psychomotor stimulant activity in mice. Repeated (3 days) daily dosing of **43** increased extracellular cortical acetylcholine in rats, whereas acute administration increased cortical extracellular signal-regulated kinase and cAMP response element-binding protein phosphorylation in mice, neurochemical and biochemical events relevant to cognitive function. Compound **43** increased cortical phosphorylation of the inhibitory residue (Ser9) of glycogen synthase kinase-3, a primary tau kinase associated with Alzheimer's disease pathology. In addition, continuous infusion of **43** in tau/amyloid precursor protein transgenic AD mice reduced spinal tau hyperphosphorylation. Compound **43** exhibited a preclinical efficacy profile that included (1) PD−PK discordance consistent with prolonged biochemical signaling germane to synaptic plasticity and enhanced cognition, (2) maintenance of efficacy with concurrent use of an AChEI, and (3) lack of nicotine-like abuse liability and CNS stimulatory activity. These findings show that targeting α7 nAChRs may have potential utility for symptomatic alleviation and slowing of disease progression in the treatment of Alzheimer's disease.

In clinical trials,[63] **43** was well tolerated over the tested single (1−100 mg) and multiple (2−15 mg once daily for 7 days) dose range; however, it exhibited nonlinear pharmacokinetics. Its development was discontinued in 2009.

1.5. Monocyclic Amines. *5-(Morpholin-4-yl)pentanoic Acid 4-(Pyridin-3-yl)phenyl)amide (WAY-317538)*[64]



44

1-[6-(4-Fluorophenyl)pyridin-3-yl]-3-[4-(piperidin-1-yl)butyl]-urea (WYE-103914).[67] *N*-{4-[4-(2,4-Dimethoxyphenyl)piperazin-1-yl]butyl}-4-pyridin-2-ylbenzamide (**46**) was identified as a weak partial agonist of α7 nAChRs (EC_{50} = 2.8 μM) after high throughput screening. The number of rotatable bonds, hydrogen bond acceptors, and relatively high molecular weight could negatively impact brain permeability of the compound. After extensive exploration, three modifications were accomplished: the amide moiety was reversed providing aromatic amides; the arylpiperazine was replaced with cyclic amines such as piperidine and morpholine; a pyridin-3-yl was incorporated instead of a pyridin-2-yl. Compound **44**[64] was developed within a Siena Biotech−Wyeth collaboration and chosen to be evaluated in in vivo efficacy models based on its generally good in vitro profile, ease of synthesis, and selectivity on a related panel of nicotinic (α1*, α3*, α4β2) and highly homologous 5HT$_{3A}$Rs. When the compound was tested at 10 μM in a panel of ∼70 binding sites including all major classes of neurotransmitter, growth factor, and peptide receptors, no significant activity was observed except at the histamine H_3 receptor, where binding was observed leading to receptor antagonism. In vivo, **44** improved performance in rodent behavioral assays of cognitive function and perceptual processing, producing enhancement of normal memory performance. The ability to attenuate pharmacologically induced deficits via either the glutamatergic or cholinergic system was demonstrated as well. Treatment with **44** (3 mg/kg, ip) minimized spontaneous decay of episodic memory in a novel object recognition task in rats; the compound was able to reverse both a scopolamine and MK-801-induced deficit in the pharmacological models for these recognition memory tests.[65] To further improve both potency and selectivity, the more basic piperidine was chosen as a cationic center instead of morpholine in compound **47**, and the chain length between cationic center and hydrogen bond acceptor was increased by the addition of a nitrogen yielding urea **48**. Compound **49** containing pyridin-2-yl fragment showed improved selectivity against the homologous

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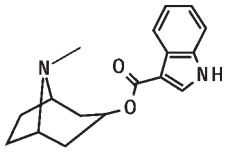
ganglionic receptor $\alpha 3^*$ and reduction of cytochrome P450 2D6 inhibition. Given that lipophilicity tends to be one of the major factors in molecular recognition by the cytochrome family of enzymes,[66] a number of analogues, where pyridine replaced the first phenyl ring of the biaryl system, were synthesized. The pyridine nitrogen was maintained, potentially pointing to the same binding area as in compound **49**. Considering the overall excellent spectrum of activity and selectivity shown, compound **45** (Figure 7)[67] was selected for further studies. Compound **45** displayed efficacy in assays of cognitive function and perceptual processing, showing an ability to attenuate pharmacologically induced deficits via the glutamatergic system. It reversed MK-801 induced deficits in both the novel object recognition and prepulse inhibition models with a minimum efficacious dose of 3 mg/kg in spite of the relatively moderate brain to plasma ratio 0.3. Unlike **44**, for which efficacy was observed after ip administration, activity of **45** was observed in both models after oral administration.

1.6. Miscellaneous. *8-Methyl 8-Azabicyclo[3.2.1]octan-3-yl)-(1H)-indole-3-carboxylate (Tropisetron)*[68]



50

Since both $\alpha 7$ nAChRs and $5HT_3$Rs belong to the ligand-gated ion channel family, there are a number of $5HT_3$R ligands with affinity and functional activity at $\alpha 7$ nAChRs and vice versa. The $5HT_3$R antagonist (K_i = 5.3 nM) **50**, which is available in Europe for the treatment of emesis, is a potent and selective partial agonist (K_i = 6.9 nM, EC_{50} = 1.3 μM, E_{max} = 36%) for the $\alpha 7$ nAChR.[68] Its unremarkable safety profile can be interpreted as demonstrating the safety of both $5HT_3$R antagonist and $\alpha 7$ nAChR partial agonist mechanistic approaches. The discovery that **50** is also a potent partial agonist for $\alpha 7$ nAChRs gives cause for the re-examination of both clinical and preclinical findings with this compound, particularly when **50** displayed pharmacological effects different from other $5HT_3$R antagonists. It was reported that the $5HT_3$R antagonists **50** and ondansetron had qualitatively different results in learning and memory paradigms in rats;[69] **50**, but not the selective 5-HT_3 receptor antagonist ondansetron, attenuated PCP-induced cognitive deficits in mice, and this effect of **50** was blocked by coadministration of the selective $\alpha 7$ nAChR antagonist MLA.[70] By use of [^{11}C]CHIBA-1001 and PET imaging techniques, it was found that **50**, but not ondansetron, after a single oral administration (5, 10, or 20 mg), binds to $\alpha 7$ nAChRs in the intact human brain in a dose-dependent manner. All of these results substantiated a clinical trial of **50** in patients with cognitive deficits in schizophrenia.[71] Compound **50** (10 mg/day for 8 weeks), but not placebo, significantly improved auditory sensory gating P50 deficits in patients with schizophrenia and had a significant impact on the sustained visual attention in nonsmoking patients. Overall, the clinical study suggests that the $\alpha 7$ nAChR agonist **50** might be a potential therapeutic drug for cognitive deficits in schizophrenia. Some additional clinical trials (Table 1) were conducted with **50** in patients with attention in nonsmoking

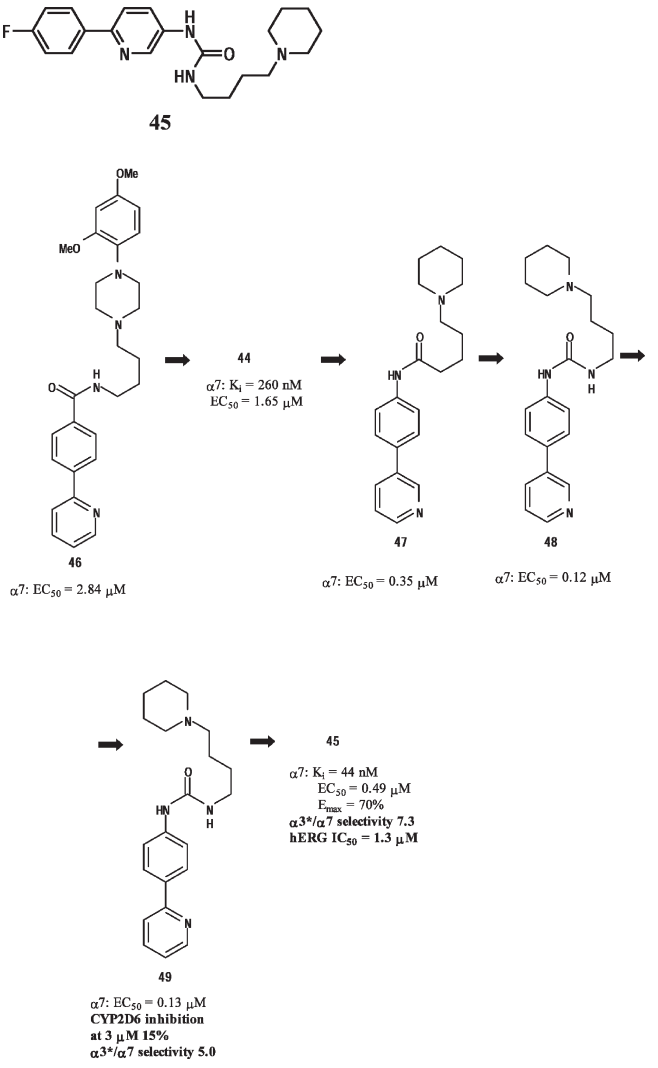


Figure 7. Compound **45**: hit−lead optimization sequence.

patients. Overall, the clinical study suggests that the $\alpha 7$ nAChR agonist **50** might be a potential therapeutic drug for cognitive deficits in schizophrenia. Some additional clinical trials (Table 1) conducted with **50** in patients with musculoskeletal and connective tissue disorders and fibromyalgia might also indicate an effect of $\alpha 7$ nicotinic partial agonism. Recently, it has been shown that **50** attenuates place aversion induced by naloxone in single-dose morphine-treated rats via the $\alpha 7$ nAChR, implicating $\alpha 7$ nicotinic receptors as viable therapeutic targets for opiate withdrawal syndrome.[78]

The $\alpha 7$ nAChR agonist AQW051 (Novartis, structure not disclosed) is currently in phase II clinical trials in Alzheimer's disease and schizophrenia. Targacept has announced separate phase II clinical studies of the $\alpha 7$ nAChR modulator TC-6987 (structure not disclosed) for disorders characterized by inflammation, one in asthma and one in type 2 diabetes. The pharmacological characteristics of these compounds have not been disclosed.

Affinities to $\alpha 7$ nAChRs and 5-HT_3Rs for the advanced compounds are summarized in Table 2 to provide a quick guide for their selectivity.

Table 1. Clinical Trials Conducted with Tropisetron

study	therapeutic group	condition	design	treatment	pop no.	conclusions/objectives
50 in osteoarthritis: the Freiburg and Posnan study[72]	musculoskeletal and connective tissue disorders	osteoarthritis	open; pooled/meta-analysis	Freiburg study: **50**, 5 mg i.art.; **50**, 5 mg i.art. on d 1, 3, and 5; Posnan study: **50**, 5 mg i.art. on d 1 and 3	12	**50** appeared to provide pain relief in patients with osteoarthritis of the knee with inflammatory reactions.
50 in tendopathies[72]	musculoskeletal and connective tissue disorders	arthropathy	double-blind; randomized	**50**, 2 mg i.art.; prilocaine, 10 mg i.art.	40	**50** had a longer effect than prilocaine on resting pain and pain on movement in patients with tendopathies or periarthropathies.
50 in tendopathies[73]	musculoskeletal and connective tissue disorders	tendinitis	double-blind; randomized	**50**, 2 mg i.art.; prilocaine, 10 mg i.art.	40	**50** had a longer effect than prilocaine on resting pain and pain on movement in patients with tendopathies or periarthropathies.
50 vs dexamethasone/lidocaine in periarthritis[74]	musculoskeletal and connective tissue disorders	arthritis	comparative; double-blind; multicenter; randomized	**50**, 5 mg by local injection; dexamethasone, 10 mg + lidocaine by local injection	40	**50** was as effective as dexamethasone/lidocaine for the treatment of periarthritis.
50 in fibromyalgia[75]	pain	fibromyalgia	double-blind; multicenter; placebo-controlled; randomized	**50**, 5 mg iv bolus o.d. × 5 d; placebo	21	**50** was well tolerated and effective in relieving pain in patients with fibromyalgia.
50 in fibromyalgia[76]	pain	fibromyalgia	open	**50**, 5 mg iv bolus × 5 y	68	**50** improved fibromyalgia pain in patients with or without depression.
50 in myofascial pain[77]	pain	pain, myofascial syndrome	multicenter; open	**50**, 5 mg/d injected into trigger point × 7 d	20	Local injections of **50** relieved pain in trigger and tender points.

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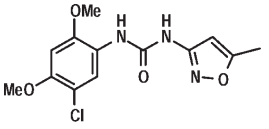
2. POSITIVE ALLOSTERIC MODULATORS (PAMS)

As an alternative to activation of a receptor with an exogenous orthosteric agonist, positive allosteric modulators (PAMs) enhance receptor function elicited by the endogenous ligand without directly activating or desensitizing the target receptor.[79] There are differences in the pharmacological profiles of positive allosteric modulators of the α7 nAChRs versus orthosteric modulators.[80,81] Type I PAMs increase the apparent peak amplitude agonist-evoked responses with minor effects on current desensitization/deactivation. For type II PAMs, peak current is dramatically increased and there is a significant prolongation of the current decay, suggesting attenuated desensitization/deactivation. The ramification on safety profiles of chronic treatment with agonists (orthosteric modulators) affecting α7 nAChRs is not yet clear; the benefit of this approach may be suboptimal because of the unknown long-term impact of sustained activation and desensitization of the nAChRs. In this context, allosteric modulation of the α7 nAChR was introduced as a novel therapeutic principle for treating cognitive dysfunction associated with various forms of dementia and schizophrenia without the potential downside of sustained orthosteric agonism of nicotinic receptors. However, according to recent studies,[82] repeated administration of α7 nAChR orthosteric agonists leads to significantly increased [^{125}I]Bgt binding, not only in the prefrontal regions as seen with acute treatment but also in the parietal cortex and hippocampus. Such up-regulation observed with orthosteric agonists of the α7 nAChRs does not occur with PAMs.

1-(5-Chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea (PNU-120596)[83]



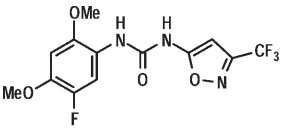
51

Compound **51**,[83] discovered in high-throughput screening, increased peak agonist-evoked currents mediated by human wild-type receptors expressed in *Xenopus* oocytes and in rat hippocampal neurons. It also demonstrated a pronounced prolongation of the evoked response in the continued presence of agonist. Compound **51** produced no detectable change in currents mediated by $\alpha4\beta2$, $\alpha3\beta4$, and $\alpha9\alpha10$ nAChRs. Compound **51** increased the channel mean open time of α7 nAChRs but had no effect on ion selectivity and relatively little, if any, effect on unitary conductance. Subsequent application of **51** on desensitized receptors in the continued presence of nicotine resulted in a reactivation of the agonist-bound receptor. Cotreatment of neurons with both **51** and the selective α7 nAChR antagonist MLA (10 nM) abolished the ACh-evoked current, indicating that **51** was acting at α7-containing nAChRs. When applied to acute hippocampal slices, **51** increased the frequency of ACh-evoked GABAergic postsynaptic currents measured in pyramidal neurons; this effect was suppressed by tetrodotoxin, suggesting that **51** modulated the function of α7 nAChRs located on the somatodendritic membrane of hippocampal interneurons. Systemic administration of **51** to rats improved the auditory gating deficit caused by amphetamine. Consistent with its classification as a type II PAM, **51** affects desensitization and prolongs excitatory synaptic events that could have excitotoxic consequences. Compound **51** was reported to be neurotoxic in an in vitro model,[80] although in vivo toxicity studies have not been reported for the compound.

Table 2. Affinities to α7 nAChR and 5-HT$_3$R for the Advanced Compounds

	K_i, nM	
compd	α7 nAChR	5-HT$_3$
1	92	2.5% at 10 μM
2	3	10
9	3	12
11	24	1662
12	8.8	511
13	44	2800
14	3.5	350
20	10	2
21	62	60
22	4.3	299 (IC_{50})
23	1	25% at 10 μM
27	2	20% at 10 μM
29	14	<50% at 10 μM
30	200 (K_d)	13000 (K_d)
31	11	<50% at 10 μM
32	13.5	269
38	10.8	150
43	7	4% at 10 μM
44	260	<50% at 10 μM
45	44	<50% at 10 μM
50	6.9	5.3

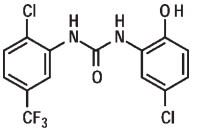
1-(5-Fluoro-2,4-dimethoxyphenyl)-3-[3-(trifluoromethyl)-isoxazol-5-yl]urea (PHA-758454)[84]



52

To establish an initial SAR around **51**, a library of closely related *N*-aryl-*N*′-heteroarylureas were screened and analyzed. Optimization resulted in compounds with enhanced potency and improved physical and ADME properties. Compound **52**[84] maintained selectivity versus other nAChRs and was selected for further characterization. In the presence of ACh, **52** enhanced evoked calcium currents in rat hippocampal neurons. In a rat model of impaired sensory gating, **52** reversed amphetamine induced disruption of hippocampal auditory gating at 0.1 and 0.3 mg/kg.

1-(5-Chloro-2-hydroxyphenyl)-3-(2-chloro-5-trifluoromethylphenyl)urea (NS1738)[85]



53

In the presence of ACh, **53**[85] produced a marked increase in the current flowing through α7 nAChRs, as determined in both

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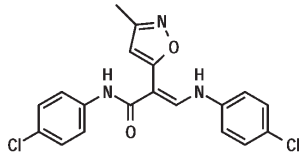
oocyte electrophysiology and patch-clamp recordings from mammalian cells. Compound **53**, a type I PAM, increased the peak amplitude of ACh-evoked currents at all concentrations with only marginal effects on the desensitization kinetics of α7 nAChRs. Mechanistically, **53** modulates the activity of the α7 nAChR by facilitating the energetic coupling between agonist binding and ion channel gating, thereby increasing the receptor open probability at all ACh concentrations. However, this enhanced efficiency of the binding-gating coupling is dissociated from the energetics of the desensitization process, which proceeds with nearly unaltered kinetics. Compound **53** (10 and 30 mg/kg) improved performance to the same extent as (−)-nicotine in the social recognition test, a model of short-term memory, and it reversed the cognitive impairment induced by (−)-scopolamine of acquisition of a water-maze learning task (at 30 mg/kg), a model of long-term spatial memory.

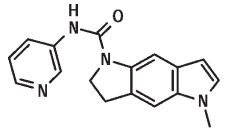
***N*-(4-Chlorophenyl)-3-(4-chlorophenylamino)-2-(3-methylisoxazol-5-yl)acrylamide (XY4083)**[80]



54

Compound **54** was developed on the hypothesis that the $GABA_A$ and α7 nAChR exhibit sufficient homology to allow the discovery of compounds that simultaneously modulate both receptors. The above compound increased the apparent potency of ACh by 2.7-fold in oocytes expressing the human α7 nAChR, potentiated EC_5 nicotine-evoked currents at α7 nAChRs in oocytes while preserving the rapid activation and deactivation kinetics of the native channel. It did not reverse desensitization evoked by extended exposure to nicotine. Compound **54** did not induce modulation of EC_5-evoked currents at human $\alpha4\beta2$, rat $\alpha3\beta4$, and mouse $\alpha1\beta1\gamma\delta$ nAChR subtypes or human 5-HT_{3A} receptors expressed in oocytes and evoked low efficacy concentration dependent positive modulation of submaximal GABA-evoked currents at human $GABA_A$ $\alpha1\beta2\gamma2L$ receptors expressed in oocytes. Compound **54** was active in three rodent models relevant to cognition and schizophrenia: sensory gating deficits in a DBA2 mouse at 0.3 mg/kg, MK-801-induced hyperlocomotion in NSA mice at 0.3−3 mg/kg, and the eight-arm radial maze in rats at 3 mg/kg ip.

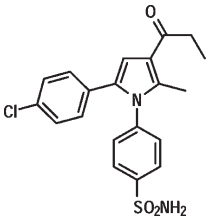
5-Methyl-*N*-(pyridin-3-yl)-2,3-dihydropyrrolo[2,3-*f*]indole-1-carboxamide (SB-206553)[86]



55

The 5-$HT_{2B/C}$ receptor antagonist **55**[86] was identified as PAM[87] in a randomized screening effort and was further confirmed and characterized using different functional assays of α7 nAChR activation, both in a recombinant cell line and natively expressed receptors in hippocampal slices. Compound **55** produced an 8-fold potentiation of the evoked calcium signal in the presence of an EC_{20} concentration of nicotine and a corresponding EC_{50} of 1.5 μM for potentiation of EC_{20} nicotine responses in GH4C1 cells expressing the α7 receptor. Compound **55** was devoid of direct α7 receptor agonist activity and selective against other nicotinic receptors. Native nicotinic receptors in CA1 stratum radiatum interneurons of rat hippocampal slices were activated by ACh (200 μM), an effect that was entirely blocked by the α7-selective antagonist MLA. Compound **55** does not share the profound prolongation of desensitization kinetics with **51** and is closer to a type I PAM. In behavioral assays, **55** reversed MK-801-disrupted prepulse inhibition, indicating that other α7 nAChR PAMs may be active in a model of sensorimotor gating relevant to schizophrenia pathology. Subsequently, it was demonstrated that the reversal of MK-801-disrupted prepulse inhibition by **55** was attenuated by MLA. This supports the notion that the in vivo pharmacological activity of **55** is driven by its α7 PAM profile and not its 5-$HT_{2B/C}$ receptor antagonism profile.

4-[5-(4-Chlorophenyl)-2-methyl-3-propionyl-1*H*-pyrrol-1-yl]-benzenesulfonamide (A-867744)[88]



56

Compound **56**[88] was discovered by optimization of a hit that was identified in high-throughput screening. In oocytes expressing α7 nAChR, **56** potentiated ACh-evoked currents, with an EC_{50} of 1 μM. In the presence of **56**, ACh concentration responses were potentiated by increases in potency, Hill slope, and maximal efficacy. The compound, as type II PAM, not only enhances the ACh-evoked currents but also slows the desensitization profile of agonist responses.[89] When examined in rat hippocampus CA1 stratum radiatum interneurons or dentate gyrus granule cells, **56** (10 μM) increased ACh-evoked α7 currents and recovery from inhibition/desensitization and enhanced spontaneous inhibitory postsynaptic current activity. Compound **56** did not displace the binding of [^{3}H]MLA to rat cortex α7* nAChRs but displaced the binding of the agonist **57** in rat cortex, with a K_i of 23 nM. Compound **56** neither increased agonist-evoked responses nor displaced the binding of **57** in an α7/5-HT_3 chimera, suggesting an interaction distinct from the α7 N-terminus or M2−M3 loop. In a panel of receptor binding assays for >70 diverse neurotransmitter receptor and ion channel sites (CEREP), no significant interaction at any of the targets (>50% displacement of test ligand) was observed at the screening concentration of 10 μM. Since **56** demonstrated acceptable animal pharmacokinetics and safety profiles, it was tested in vivo in the DBA/2 mouse. In a paired auditory stimulus paradigm, **56** (0.1−10.0 μmol/kg, ip) improved sensory gating deficits, reducing the ratio of the response to test stimulus relative to the preceding response to conditioning stimulus (T/C ratio).

SLURP-1. SLURP-1, secreted mammalian Ly-6/uPAR-related protein 1, that is encoded by the SLURP-1 gene and structurally similar to the snake venom toxin α-bungarotoxin has been identified as a modulator of the human α7 nAChR.[90] The lack of action of SLURP-1 in the absence of acetylcholine and its

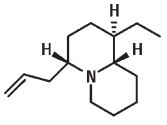
important potentiation of the acetylcholine response suggest that SLURP-1 acts as a positive allosteric effector at the α7 receptor. SLURP-1 (200 pM and 20 nM) enhanced the amplitude of Ach-evoked currents in *Xenopus* oocytes expressing recombinant human α7 nAChRs by 421% and 1214%, respectively. A concentration−response curve of ACh in the presence of 200 pM SLURP-1 indicates that the protein increases both ACh potency and efficacy at the α7 nAChR. Since SLURP-1 potentiates the human α7 nAChRs that are present in keratinocytes, the PAM was identified as a secreted epidermal neuromodulator which is essential for both epidermal homeostasis and inhibition of TNF-α release by macrophages during wound healing.

3. ANTAGONISTS

Although extensive efforts have been taken to identify selective α7 nAChR agonists, the development of selective antagonists is limited by comparison. Natural toxins α-bungarotoxin (α-Bgt) and methyllycaconitine (MLA) are two frequently used α7 nAChR selective antagonists. α7 nAChR selective antagonists recently have been explored as potential treatments for non-small-cell lung cancer[91] and for organophosphorus nerve agent intoxication.[92]

DECCSNPACRLNNPHDCRRR (Amino Acid Sequence) (α-CtxArIB[V11L,V16D]).[94] Cone snails (genus *Conus*) produce a vast array of peptide toxins that target ion channels, including nAChRs, with exceptional selectivity.[93] The conopeptide family that targets nAChRs, α-conotoxins (α-Ctxs), consists of small (13−19 residue) peptides, internally cross-linked by a pair of disulfide bridges. α-Conotoxins target narrow ranges of nAChR subtypes, and sometimes individual subtypes, with an unprecedented degree of specificity. Since α-Ctxs are short peptides, they and their analogues may be synthesized by standard peptide synthesis techniques. Optimization of peptide from *Conus arenatus* resulted in the selective analogue α-CtxArIB[V11L,V16D]) (**58**),[94] which was 800- to >10000-fold more potent against α7 (IC_{50} = 1.09 nM) than all other nAChR subtypes expressed in *Xenopus* oocyte with minute-scale on-rate and off-rate kinetics. When tested against native nAChR subtypes in displacement binding assays, it also showed low nanomolar affinity for α7 and poor to no affinity for non-α7 nAChR subtypes. Activity of **58** on native nAChRs was assessed in competition binding studies using mouse brain and *Torpedo* electroplax homogenates. Compound **58** displaced [^{125}I]α-Bgt binding in mouse hippocampal membranes with a K_i of 7.04 nM. Compound **58** interacts with five ligand binding sites per α7 receptor, and occupation of a single site is sufficient to block function.

(−)-4-Allyl-1-ethyloctahydroquinolizine (Quinolizidine (−)-1-epi-207I)[96]



59

Extracts from the skin of certain poison frogs provide a variety of pharmacologically active alkaloids, and more than 500 alkaloids have been isolated to date.[95] The 1,4-disubstituted quinolizidine **59**[96] was discovered by study of amphibian bicyclic alkaloids in *Xenopus laevis* oocytes expressing major types of

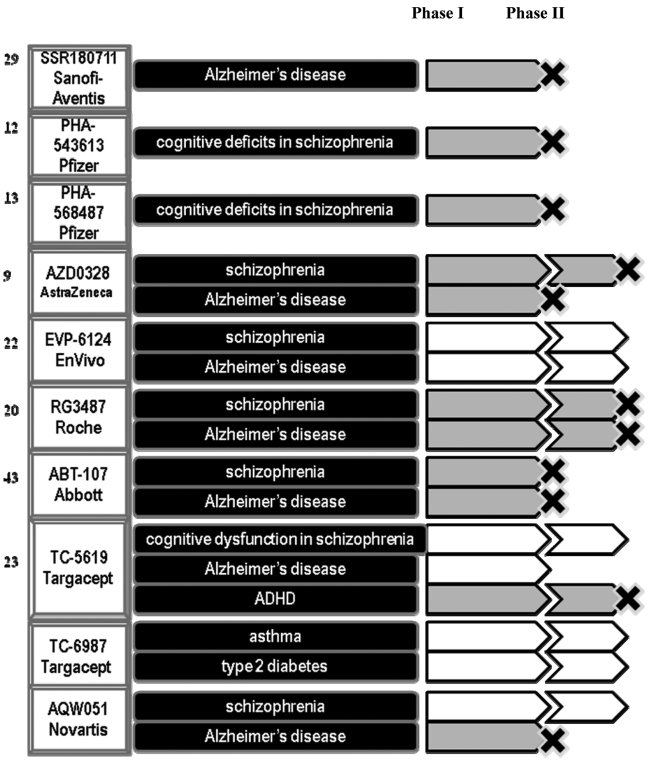
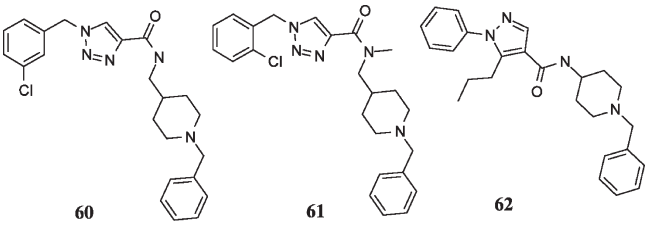


Figure 8. α7 nAChR product development pipeline. Gray bars with black cross indicate that development of the drug candidates was discontinued. White bars designate successful or ongoing clinical trials.

neuronal nicotinic receptors ($\alpha4\beta2$, $\alpha7$, $\alpha3\beta2$, $\alpha3\beta4$, and $\alpha4\beta4$). It selectively blocked α7 acetylcholine-elicited currents (IC_{50} = 0.6 μM) with an 8.7-fold higher sensitivity than blockade of $\alpha4\beta2$ receptor responses (IC_{50} = 5.2 μM) and a 14.7-fold higher blockade than that of $\alpha3\beta4$ receptor responses (IC_{50} = 8.8 μM). (−)-4-allyl-1-ethyloctahydroquinolizine is a noncompetitive inhibitor of α7 nAChRs.

Imidazole and Triazole Carboxamides



60 **61** **62**

Recently, two series of selective α7 nAChR antagonists were described.[97] The functional activity of compounds **60**, **61**, and **62** was determined by electrophysiological experiments on *Xenopus* oocytes expressing human α7 nAChRs. These three compounds inhibited acetylcholine-evoked receptor responses in a dose-dependent manner with IC_{50} values of 11.9, 3.7, and 18.9 μM for compounds **60**, **61**, and **62**, respectively. The selectivity of compounds **60** and **62** was measured against three receptors: neuronal $\alpha4\beta2$ nAChRs, muscle-type nAChRs, and $5HT_3$Rs. At 10 μM, compound **60** exhibited 82.5% displacement of radioligand to α7 nAChRs and 18.8% and 8.4% to neuronal $\alpha4\beta2$ nAChRs and $5HT_3$Rs, respectively. Similarly, compound **62** showed displacement of 82.5% to α7, 1.3% to $\alpha4\beta2$, and

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14.3% to $5HT_3$Rs. Both compounds exhibited no detectable binding to the muscle-type nAChRs at 10 μM. Antagonists **61** and **62** were tested in a toxicity animal model using the organophosphorus nerve agent diisopropyl fluorophosphate (DFP) to investigate their antiseizure activity. Compared with DFP controls, pretreatment with compounds **61** and **62** antagonized DFP-induced seizure-like behaviors over a 2 h period after injection by 93.4% and 91.2%, respectively. The results suggest that these compounds could provide neuroprotection against seizure-like behaviors induced by DFP and therefore may be useful for treatment of organophosphorus nerve agent intoxication.

4. CONCLUSION

Intense research of α7 nAChRs for the past decade has revealed their critical roles in cognitive processes, neuroprotection, sensory gating, and cytokine-mediated inflammation. Discovery and development of structurally diverse selective ligands have motivated the initiation of clinical trials in neuropathological conditions and diseases such as AD, schizophrenia, and intractable immune and inflammatory conditions such as type 2 diabetes and asthma (Figure 8). Therapeutic agents used to treat AD today, such as acetylcholine esterase inhibitors and glutamate-NMDA receptor antagonists, only provide modest symptomatic relief. Therefore, a major challenge in developing improved AD pharmacotherapies is identifying disease-modifying mechanisms, in addition to symptomatic reducton. Recently revealed results indicate that α7 nAChR agonism may provide both symptomatic and disease-modifying efficacy in the treatment of AD. A few α7 nAChR agonists (**22**, **23**, **50**) demonstrated positive results in clinical trials. However, the termination of promising clinical candidates, such as **9**, **12**, **13**, **20**, reflects the challenges of developing new agents for the treatment of cognitive impairment in AD and in schizophrenia. While the clinical utility of α7 nAChR agonists continues to be evaluated, results of clinical trials appearing in the peer reviewed literature are still anticipated. Continued discovery and evaluation of PAMs with novel areas of chemical space provide an opportunity to improve our understanding of this drug target, whereas further development of pharmaceutically relevant antagonists might expand the therapeutic potential of α7 nAChRs.

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BIOGRAPHIES

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Jason D. Speake is the Group Leader of Medicinal Chemistry at Targacept, Inc. in Winston-Salem, NC. Jason obtained his Ph.D. in 1997 at Indiana University in the laboratories of Paul Grieco, accomplishing the total synthesis of biologically interesting natural products and analogues. He then moved to the medicinal chemistry group at GlaxoWellcome (later GlaxoSmithKline) in North Carolina, where he worked primarily in CNS mediated metabolic disorders. In 2008, Jason transitioned to Targacept to lead the medicinal chemistry group in the discovery of therapeutic agents targeting neuronal nicotinic receptors.

Daniel Yohannes, Ph.D., is the Senior Director of Drug Discovery at Targacept, where he is responsible for the functions of molecular design, medicinal chemistry, research compound management, and chemical process research. Daniel completed his Ph.D. in the synthesis of natural products in 1991 at Purdue University, IN, after which he completed a National Institutes of Health funded postdoctoral position at Yale University, CT. He then spent 8 years with Pfizer in Neuroscience Medicinal Chemistry, the majority of which was spent in drug discovery in ligand-gated ion channels (nicotinic and $GABA_A$ receptors). He later took positions of increased responsibilities as Director of Medicinal Chemistry at Infinity Pharmaceuticals and then as Director of Chemistry at ArQule, Inc. before coming to Targacept, where he has been for 6 years.

ABBREVIATIONS USED

ACh, acetylcholine; AD, Alzheimer's disease; ADHD, attention deficit/hyperactivity disorder; α-Bgt, α-bungarotoxin; nAChR, nicotinic acetylcholine receptor; CYP, cytochrome P; DBA/2, dilute brown non-agouti; DMTS, delayed matching-to-sample test; GABA, γ-aminobutyric acid; hERG, human ether-a-go-go-related gene; JAK, Janus kinase; ip, intraperitoneal injection; MATRICS, measurement and treatment research to improve cognition in schizophrenia; MED, minimally effective dose; MLA, methyllycaconitine; PAM, positive allosteric modulator; PET, positron emission tomography; po, oral administration; PPI, prepulse inhibition; SHR, spontaneously hypertensive rat; SH-SY5Y, human neuroblastoma cell line; *th(tk−)/th(tk−)*, homozygous transgenic mouse

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