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Structure–activity relationship studies of SEN12333 analogues: Determination of the optimal requirements for binding affinities at α7 nAChRs through incorporation of known structural motifs

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ABSTRACT

Alpha7 nicotinic acetylcholine receptors (nAChRs) have implications in the regulation of cognitive processes such as memory and attention and have been identified as a promising therapeutic target for the treatment of the cognitive deficits associated with schizophrenia and Alzheimer's disease (AD). Structure affinity relationship studies of the previously described α7 agonist SEN12333 (**8**), have resulted in the identification of compound **45**, a potent and selective agonist of the α7 nAChR with enhanced affinity and improved physicochemical properties over the parent compound (SEN12333, **8**).

1. Introduction

Neuronal nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated cation channels that have generated extensive interest as potential therapeutic targets for the treatment of cognitive disorders [1–3]. There exist multiple subtypes of nAChRs where each subtype is formed from either a homo- or heteropentameric combination of twelve possible subunits: α2–α10 and β2–β4. The homomeric α7 nAChR is one of the most commonly expressed nicotinic receptor subtypes in the human brain and is found in high levels of expression in regions associated with learning and memory such as the cerebral cortex and the hippocampus [4–6]. Experimental evidence supports the involvement of this receptor in schizophrenia and Alzheimer's disease (AD) [7,8]. Schizophrenia and AD are both chronic conditions with intense and devastating symptoms; modulators of the α7 nAChR have been extensively studied for the treatment of the cognitive deficits associated with these pathologies [4,6,9–11].

Schizophrenia is a disease defined by positive (hallucinations, delusions) and negative symptoms (reduced affect, low motivation, social withdrawal, disorganized thoughts) and cognitive impairments (learning and memory deficits, decreased attention) [12]. While positive symptoms are somewhat controlled with current medications, cognitive deficits and negative symptoms largely remain untreated. Examinations of the post-mortem brains of schizophrenic patients have revealed a reduction in α7 mRNA expression and concomitantly a reduction in the density of α7 nAChR protein [13–15]. Furthermore, polymorphisms within the α7 nAChR subunit gene *CHRNA7* have been associated with the auditory gating deficits in schizophrenia, a defect ordinarily normalized by nicotine and possibly underlying the high incidence of tobacco use among schizophrenic patients [16–18]. Selective α7

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nAChR agonists have shown excellent *in vivo* efficacy in the normalization of auditory gating in rats, indicating potential utility in the treatment of the cognitive deficits associated with schizophrenia [4,19,20].

A reduction in the expression of α7 nAChR protein has similarly been observed in the hippocampus of AD patients [21,22]. A component of β-Amyloid (Aβ) peptides, the characteristic neuritic plaques of AD thought to contribute to neurodegeneration, was found to interact with the α7 nAChR with picomolar affinity [23,24]. Exogenous nAChR agonist nicotine exhibits protective effects against the neurotoxicity of Aβ peptides, and this neuroprotection can be blocked through selective antagonism of α7 nAChRs [25]. Furthermore, utilization of siRNA transfection to inhibit α7 mRNA and protein expression, further exacerbated the toxicity of Aβ peptides in neuroblastoma SH-SY5Y cells [26]. As is consistent with such findings, selective activation of α7 nAChRs attenuated Aβ-induced cell death, and suggests a therapeutic application for α7 nAChR agonists in the treatment of AD [25,26].

Whilst α7 nAChR is a valid target with therapeutic application in schizophrenia and AD, few structural classes of selective α7 nAChR agonists have been identified, and reported ligands are primarily centred on anabaseine, quinuclidine, or diazabicyclic scaffolds [27]. One of the initial functionally α7-selective agents identified was partial agonist, dimethoxybenzylidene anabaseine (DMXB-A, **1**, Fig. 1), exhibiting only micromolar potency at α7 nAChRs with off-target activity at α4β2 nAChRs and 5-HT3 receptors [28,29]. In proof of concept trials for non-smoking schizophrenic patients, DMXB-A (**1**) exhibited an improvement in various neurocognitive measures and has progressed to Phase II studies, further providing a foundation for the therapeutic use of α7 agonists [2,30].

In relation to the pharmaceutical industry, various α7 nAChR agonists have entered clinical trials for use in the treatment of cognitive deficits of schizophrenia (CDS). An early example disclosed by AstraZeneca was the quinuclidine-derived spiro-oxazolidinone, AR-R17779 (**2**), a potent full agonist with several hundred-fold *in vitro* selectivity for rat α7 over rat α4β2 nAChRs [31]. Pharmacological profiling of AR-R17779 (**2**) *in vivo* demonstrated improvements in learning and memory in several rat models, in accordance with the expected cognition-enhancing properties of selective α7 nAChR agonists [32,33]. SR180711 (**3**) was reported by Sanofi-Aventis as a potent partial agonist of recombinant human α7 nAChRs. It displays over 250-fold selectivity for α7 over other nAChR subtypes and negligible affinity for 100 other receptors [34,35]. Phencyclidine induced cognitive deficits were shown to be normalized following SSR180711 (**3**) administration in mice which further supports the role of α7 nAChR agonists in treating CDS and AD [36,37]. SSR180711 (**3**) successfully entered Phase II clinical trials, however, studies were discontinued due to cataract development in subjects and a narrow therapeutic index. Additional examples of α7 nAChR agonists entering clinical trials for the treatment of CDS include TC-5619 (**4**, Phase II), ABT-107 (**5**, Phase I), and EVP-6124 (**6**, Phase III) [6,38–40]. Despite showing initial success, TC-5619 (**4**) and ABT-107 (**5**) have since been withdrawn from the clinic, however, EVP-6124 (**6**) has successfully progressed to Phase III clinical trials and suggests that α7 nAChR agonist can be safely targeted in the clinic. It is evident that known α7 ligands display relatively little structural diversity and have likely been developed through optimization of a common chemotype. The majority of these ligands therefore possess the same cross-reactivity with other sites, such as activity at hERG channels.

High-throughput screening by Siena Biotech and Wyeth led to the discovery of piperazine **7** (Fig. 2) as a novel chemotype with weak partial agonist activity at α7 nAChRs, further investigation of the piperazine, biaryl, and amide regions of compound **7** culminated in the discovery of SEN12333 (**8**) [41]. SEN12333 (**8**) is a potent and selective α7 nAChR agonist, displaying exceptional selectivity for α7 over other nAChR subtypes, 5-HT3 receptors, and hERG channels [41,42]. Aside from its favourable *in vitro* profile, SEN12333 also exhibited acceptable bioavailability and good brain penetration in rats [42]. Initial investigations of SEN12333 in animal models of episodic memory unveiled its ability to reverse both scopolamine- and MK-801-induced amnesia [41,42].

The development of SEN12333 (**8**) was centred on simultaneous improvement of potency and drug-like properties. Accordingly, only limited structure–activity relationships are evident for this class of α7 nAChR ligands. Modification of the morpholine functionality contained within compound **8** revealed branched acyclic amines to result in decreased potency while small, aliphatic azacycles appear to be optimal, however, few examples of these are reported [41]. Brief exploration into the replacement of the arylanilide with other aromatic moieties showed little effect on α7 nAChR activity, however, biaryls were generally preferred over

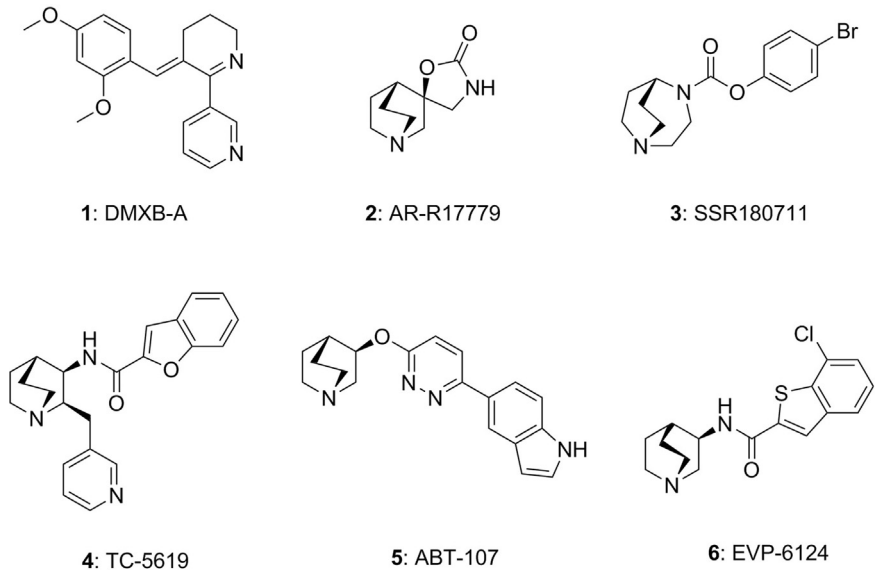

Fig. 1. Selected α7 nAChR agonists evaluated in preclinical and clinical studies.