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Review

Nicotinic ligands as multifunctional agents for the treatment of neuropsychiatric disorders

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ABSTRACT

The challenges associated with developing more effective treatments for neurologic and psychiatric illness such as Alzheimer's disease and schizophrenia are considerable. Both the symptoms and the pathophysiology of these conditions are complex and poorly understood and the clinical presentations across different patients can be very heterogeneous. Moreover, it has become apparent that the reductionist approach to drug discovery for these illnesses that has dominated the field for decades (i.e., the development of highly selective compounds or other treatment modalities focused on a very specific pathophysiologic target) has not been widely successful. Accordingly, a variety of new strategies have emerged including the development of "multitarget-directed ligands" (MTDLs), the development and/or identification of compounds that exhibit "multifunctional" activity (e.g., pro-cognitive plus neuroprotective, pro-cognitive plus antipsychotic activity), "repurposing" strategies for existing compounds that have other clinical indications, and novel "adjunctive" treatment strategies that might enhance the efficacy of the currently available treatments. Interestingly, a variety of ligands at nicotinic acetylcholine receptors (nAChRs) appear to have the potential to fulfill one or more of these desirable properties (i.e., multifunctional, repurposing, or adjunctive treatment potential). The purpose of this review (while not all-inclusive) is to provide an overview of a variety of nAChR ligands that demonstrate potential in these categories, particularly, "multifunctional" properties. Due to their densities in the mammalian brain and the amount of literature available, the review will focus on ligands of the high affinity α4β2 nAChR and the low affinity α7 nAChR.

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Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's Disease; DMTS, delayed match to sample; MLA, methyllycaconitine; NHP, non-human primate; NOR, spontaneous novel object recognition.

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1. Introduction

The rising prevalence of neuropsychiatric illnesses is a major public health concern while at the same time, research and development (R&D) for new drugs to treat these conditions is declining and many pharmaceutical companies have abandoned this field of research altogether [1,2]. There are a number of cited reasons for this decline in R&D and they include the low success rate for clinical approval of novel treatments, increased time and costs associated with the regulatory burden, litigation-related concerns with drugs that do reach the market, and the wider availability of generic drugs which reduces profits for companies that heavily invest in R&D [3]. Even during the most aggressive periods of R&D in the last 15 years, there has been a paucity of truly new chemical entities developed in the pharmaceutical industry [4] and this has been particularly apparent in the field of neurology and psychiatry.

It has also become increasingly evident that the reductionist approach to modern drug discovery that has dominated the field for decades (i.e., the development of highly selective compounds or other treatment modalities focused on a very specific pathophysiologic target) has not been widely successful [5], especially for the

Table 1
Representative nAChR ligands with multifunctional activity

Compound Name	nAChR subtype	Receptor Effect	Cognitive Domain Enhanced	Additional Properties	References
ABT-418	α4β2	agonist	attention, working memory, spatial learning, associative learning	Analgesic, Neuroprotective (glutamate excitotoxicity)	[49,54,57,155]
ABT-594	α4β2	agonist	attention, working memory	analgesic	[82,158,159]
ABT-894	α4β2	agonist	attention, executive function	analgesic	[94,160]
AZD 1446 (TC-8863)	α4β2	agonist	attention, working memory, spatial learning/ memory		[161,162]
SIB-1508Y	α4β2	agonist	attention, short-term memory, working memory	Antidepressant	[55,58]
Sazetidine-A	α4β2	agonist, 'silent desensitizer'	attention	analgesic, antidepressant	[178,179,180]
NS9283	α4β2	PAM	attention, social recognition, spatial reference memory	Sensorimotor gating	[130]
AZD-3480 (TC-1734)	α4β2	partial agonist	attention, episodic memory, working memory and executive function	neuroprotective (glutamate), antidepressant	[181,182]
Varenicline	α4β2	partial agonist (+ α7 agonist)	attention, recognition memory, working memory		[69,151]
ABT-107	α7	agonist	attention, episodic, working and recognition memory, executive function	Neuroprotective (6-OHDA lesion model), sensory gating	[21,22,164]
AR-R1779	α7	agonist	working memory, social recognition,		[51,56,165]
GTS-21 (DMXBA)	α7	partial agonist (+ weak α4β2 antagonist)	associative learning, working memory, recognition memory	P50 sensory gating	[23,47,109]
SEN-12333	α7	agonist	attention, episodic, object and memory, executive function	Neuroprotective (quisqualate lesion model), Sensorimotor gating (PPI)	[112]
Tropisetron	α7	partial agonist (+ 5HT3 antagonist)	attention, recognition memory, spatial learning	Sensorimotor gating (PPI)	[88,102,103,111,166,167,168]
EVP-6124	α7	partial agonist (+ 5HT3 antagonist)	attention, episodic memory, working memory and executive function		66
TC-5619	α7	agonist	attention, recognition memory, executive function	Sensorimotor gating (PPI)	[64,124]
RG 3487	α7	partial agonist (+ 5HT3 antagonist)	attention, spatial learning, episodic, recognition and working memory, executive function	Sensorimotor gating (PPI)	[67]
JNJ-39393406	α7	mixed Type I & II PAM	attention, recognition memory, executive function	sensory gating	[148]
AVL-3288	α7	Type I PAM	episodic recognition memory, working memory and executive function	Neuroprotective (glutamate excitotoxicity, amyloid-β), Sensory gating	[137]
Galantamine	α7	Type I PAM + AChEI	attention, recognition memory, cognitive flexibility, spatial learning	Sensorimotor gating (PPI)	[138,169,170,171]
Genistein	α7	Type I PAM	associative learning	neuroprotective (3-Nitropropionic acid model)	[171,174]
NS1738	α7	Type I PAM	recognition memory, spatial learning, working memory and executive function		[136,171]
PNU 120596	α7	Type II PAM	recognition memory, spatial learning, working memory, cognitive flexibility	Sensory gating	[138,141,146]
Cotinine	α7	sensitizer	attention, recognition memory, working memory, executive function	Neuroprotective (amyloid), Sensorimotor gating (PPI)	[41,42,43,46,175,176,177]
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Nicotine	α4β2 + α7	agonist	attention, working memory, recognition memory	Neuroprotective (amyloid), Sensorimotor gating (PPI)	[25,26,27,28,29,30,36,183]
ABT-089	α4β2 + α6β2	α4β2 agonist + α6β2 partial agonist	attention, episodic memory, working memory, spatial learning, executive function	Neuroprotective (glutamate excitotoxicity)	[38,172,173]