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BMS-933043, a Selective α7 nAChR Partial Agonist for the Treatment of Cognitive Deficits Associated with Schizophrenia

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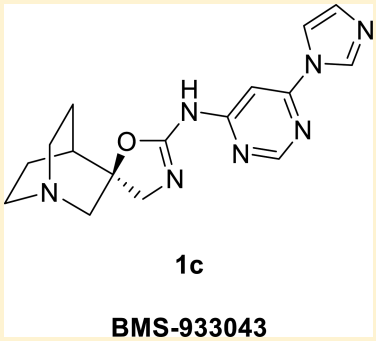
Supporting Information

ABSTRACT: The therapeutic treatment of negative symptoms and cognitive dysfunction associated with schizophrenia is a significant unmet medical need. Preclinical literature indicates that α7 neuronal nicotinic acetylcholine (nACh) receptor agonists may provide an effective approach to treating cognitive dysfunction in schizophrenia. We report herein the discovery and evaluation of **1c** (BMS-933043), a novel and potent α7 nACh receptor partial agonist with high selectivity against other nicotinic acetylcholine receptor subtypes (>100-fold) and the 5-HT_{3A} receptor (>300-fold). *In vivo* activity was demonstrated in a preclinical model of cognitive impairment, mouse novel object recognition. BMS-933043 has completed Phase I clinical trials.



KEYWORDS: *Schizophrenia, α7 neuronal nicotinic acetylcholine receptor, α7 nAChR partial agonist, quinuclidine, clinical candidate*

Schizophrenia is a severe and chronic psychiatric disorder affecting approximately 1% of the general population. The clinical features of schizophrenia include hallucinations and delusions (positive symptoms), loss of motivation and social withdrawal (negative symptoms), and cognitive impairment including deficits in executive cognitive function, selective attention, and working memory.[1] Cognitive impairment is inadequately treated by marketed antipsychotic drugs and contributes to the marked social and occupational dysfunction seen in patients. Improved cognition is one of the best predictors of improved functional outcome[2] and represents a significant unmet medical need.[3]

The pathophysiology of schizophrenia has been linked to the cholinergic neurotransmission system and, in particular, to the α7 neuronal nicotinic acetylcholine receptor (α7 nAChR).[3] nAChR subtypes transduce the acetylcholine signal in the limbic and cortical regions of the brain, where cholinergic receptors are highly expressed. Polymorphisms in the promoter region of the CHRNA7, a gene that encodes for the α7 nAChR, are linked to P50 sensory gating suppression in schizophrenics.[4,5] Additionally, post-mortem analysis of brain tissue isolated from schizophrenia patients shows reduced expression of α7 nAChRs in the hippocampus and dentate gyrus.[6]

It has been noted that nicotine, a prototypical agonist of nAChRs, improves cognitive deficits and negative symptoms associated with schizophrenia.[7] Nicotine also improves P50 auditory gating performance in schizophrenics.[8] The high rate of tobacco smoking observed in schizophrenics is thus thought to be an indication of self-medication.[9] These observations have led many groups over the past two decades to seek the development of nAChR agonists, and in particular, selective agonists of α7 nAChR to improve cognitive deficits associated with schizophrenia. Many α7 nAChR agonists have demonstrated improvement in preclinical models of memory and cognition,[10−15] and several compounds have progressed to human clinical trials, including DMXB-A (GTS-21),[16] EVP-6124,[17,18] TC-5619,[19−21] and others.[22] Of particular note, clinical efficacy has been reported for both EVP-6124[18] and TC-5619[21] in Phase II trials, although positive clinical end points were not achieved in later-stage trials. Examples of α7 nAChR agonists are shown in Figure 1.

In our program, we prioritized the development of compounds with potent α7 nAChR partial agonist effects, a profile expected to have reduced potential for receptor desensitization compared to agonists that fully activate the receptor.[23,24] Among previously published α7 receptor agonists, many have demonstrated antagonist activity at the serotonergic 5-HT_{3A} receptor. This is likely due to the high sequence homology between α7 receptors and 5-HT_{3A} receptors.[25] In fact, the marketed antiemetic 5-HT_{3A} receptor antagonist tropisetron was shown to be a potent α7 receptor partial

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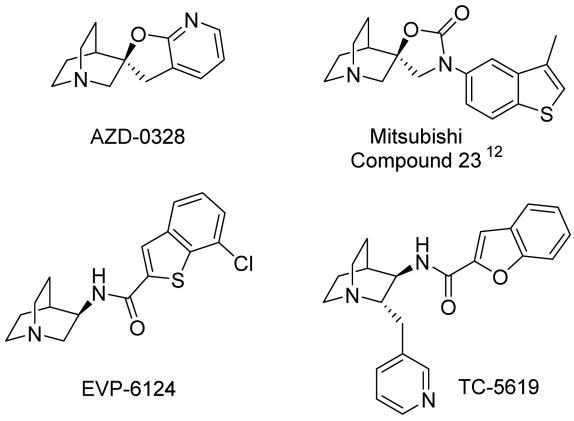

Figure 1. Examples of α7 nAChR agonists.

agonist.[26] Since 5-HT_{3A} receptor antagonism has been associated with off-target gastric side effects,[27,28] we also prioritized the development of compounds with high selectivity relative to this target.

Most of the compounds in Figure 1 are characterized by a pharmacophoric model consisting of three elements: (1) a rigid bicyclic amine, which serves as a cationic center at physiological pH, (2) an exocyclic amide, carbamate, or carbonyl biosteric heterocycle serving as a central H-bond acceptor (mimicking the ester carbonyl in ACh), and (3) a lipophilic aromatic or heteroaromatic group.[29−31] Our extensive SAR efforts[32−34] identified a novel chemotype which conformed to this pharmacophore, with (1*S*,4*S*)-quinuclidine serving as the preferred bicyclic amine and (*R*)-aminooxazoline (spiroimidate) as an isostere for the central H-bond acceptor (Figure 2).

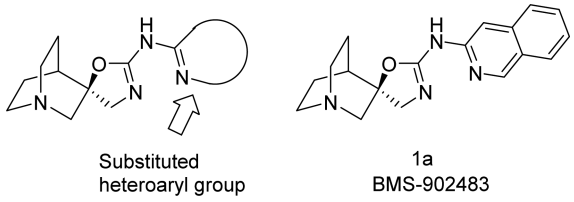

Figure 2. Structures of the quinuclidine spiroimidate chemotype and compound **1a**.

In developing compounds with optimum α7 receptor partial agonism properties and high selectivity relative to the 5-HT_{3A} receptor, we found that the choice of the heteroaryl group was an important factor. Compounds that contained 4-aminopyrimidines substituted in the 6-position with aromatic and heteroaromatic rings, and fused heteroaromatics generally provided this combination of characteristics.[32−34]

We identified BMS-902483 (**1a**) as an early example of a potent α7 nACh receptor partial agonist (Figure 2).[32] This compound bound with high potency to native rat and recombinant human α7 nAChRs and demonstrated agonist activity in a Ca^{2+} fluorescence assay (FLIPR). In whole cell voltage clamp electrophysiology experiments, **1a** showed a potent, partial agonist profile (data summarized in Table 1). Compound **1a** had no agonist or antagonist activity at other nicotinic acetylcholine receptor subtypes ($\alpha1\beta1\delta\varepsilon$, $\alpha3\beta4$, $\alpha4\beta2$) and demonstrated a 50-fold margin with respect to the binding of human 5-HT_{3A} receptors. *In vivo* evaluation of **1a** in the mouse novel object recognition (NOR) model showed this compound to be efficacious at doses of 0.1−3 mg/kg, *sc*.[32] As an indicator of potential cardiovascular safety, **1a** was evaluated for inhibition of the hERG potassium channel in a patch clamp electrophysiological assay and was found to be a moderate inhibitor (IC_{50} = 3.2 μM). At the NOR minimum effective dose (0.1 mg/kg, *sc*), **1a** was considered to possess a sufficient safety margin to advance into preclinical toxicological studies.[35] Unfortunately, in a 1 month of GLP repeat dose dog study, **1a** showed drug-related liver and kidney changes correlated with elevations in AST, ALT, and alkaline phosphatase. QT prolongation was also observed at high doses. Thus, further development of this compound was halted.[32]

In developing an alternative to **1a**, we required a candidate with reduced potential for cardiovascular liability, as measured in our hERG patch clamp assay, while maintaining target efficacy at low exposures. Since compound lipophilicity is a contributing factor to binding at the hERG channel,[36] we felt that compounds with lower lipophilicity would have the best potential to be weaker inhibitors of the hERG channel. Therefore, we used cLogP values[37] as an estimate of lipophilicity to help guide our selection process. cLogP values less than that of **1a** (1.4) were targeted.

A group of compounds that initially attracted our attention was a series of deannulated analogues of **1a**, the 6-aryl substituted 4-aminopyrimidines.[34] The prototype of this series, **1b**, exhibited a potent and selective α7 partial agonist profile (rat EP EC_{50} = 0.49 nM, peak Y_{max} 13%, area Y_{max} 49%; >800-fold selective versus the 5-HT_{3A} receptor; see Table 1).[38] However, this compound was a moderate hERG inhibitor (IC_{50} = 4.0 μM) with a cLogP value of 2.8 and would not meet our cardiovascular risk criteria. We next considered compounds **1c−h**, a group of 4-aminopyrimidines substituted in the 6-position with a five-membered heteroaryl or heterocyclic group, as shown in Scheme 1. These compounds had significantly lower cLogP values than either **1a** or **1b** (Figure 3). Compounds **1c−h** were surveyed in a single-point hERG patch clamp assay in order to quickly assess this liability. It was observed that decreasing hERG potency correlated well with the lower cLogP values (Figure 3). Among this group, **1c** (BMS-933043) had the lowest cLogP value (0.27) and hERG channel inhibition (38% at 30 μM test concentration) and was chosen for extensive *in vitro* and *in vivo* profiling.

Quinuclidine spiroimidates **1a−h** were prepared according to the methods described by Cook and co-workers[32] and are shown in Scheme 1. Briefly, treatment of borane-protected quinuclidine **2**[39−41] with benzyl chloroformate (CBZ-Cl) gave the corresponding racemic CBZ- and borane-protected amino alcohol, which was then separated into its individual enantiomers by chiral chromatography. The CBZ- and borane-protecting groups were removed from the preferred isomer (*S*)-**3**[32] in a one-pot procedure by treatment with aqueous HCl, followed by hydrogenolysis in the presence of catalytic palladium to afford the chiral amino alcohol **4** as the dihydrochloride salt. Final compounds **1a−h** were then obtained by one of two methods. Heterocyclic amines **5a−g** were converted to the corresponding intermediate dimethylimidodithioates **6a−g** by treatment under basic conditions with carbon disulfide and methyl iodide. Condensation of **4** and **6a−g** in the presence of Cs_2CO_3 then provided **1a−g**. Heterocyclic amine **5h** was alternatively converted to the isothiocyanate **6h**, which was reacted with **4** followed by ring closure with diisopropylcarbodiimide to yield **1h**.

In the α7 FLIPR assay, **1c** exhibited an EC_{50} = 23 nM (Table 1). Like **1a**, this compound was devoid of agonist (EC_{50} > 100

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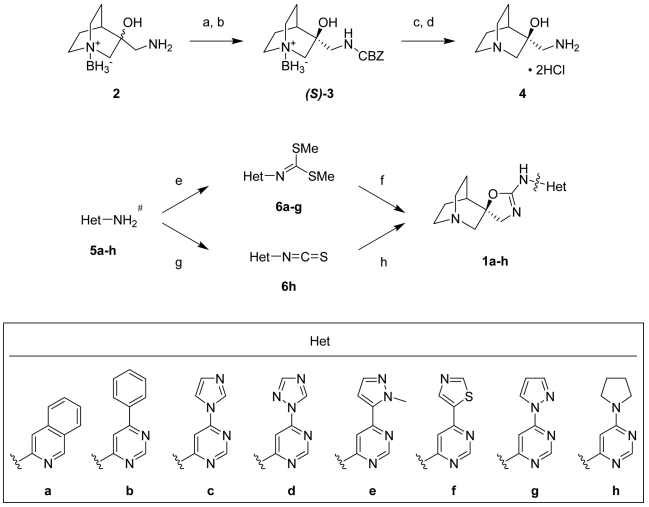
Table 1. Selected *in Vitro* Screening Data of 1a, 1b, and 1c[42]

compound		1a	1b	1c
cLogP		1.4	2.8	0.27
FLIPR rat $\alpha7$ (EC_{50}, nM)[a]		9.3 ± 5.3	11 ± 6	23 ± 10
rat $\alpha7$	BTX[b] binding (K_i, nM)	4.8		3.3
human $\alpha7$	BTX[b] binding (K_i, nM)	1.3		8.1
rat $\alpha7$ nAChR electrophysiology				
	peak Y_{max}, area Y_{max} (%)	40, 54	13, 49	27, 67
	area EC_{50} (nM)	140	0.49	100
human $\alpha7$ nAChR electrophysiology				
	peak Y_{max}, area Y_{max} (%)	26, 62		24, 78
	area EC_{50} (nM)	240		300
nicotinic ACh-related receptors (EC_{50}, μM)[c]		>100		>100
HEK293 human 5-HT_{3A} (IC_{50}, nM)[a]		480 ± 160	9200 ± 1400	8100 ± 2300
metabolic stability, % remaining (human, rat, mouse, dog, monkey)		96, 1, 89, 74, 78		91, 95, 93, 98, 100
CYP inhibition, IC_{50} (μM)[d]		>40		>30
hERG, patch clamp assay (IC_{50}, μM)		3.2	4.0	>30[e]
plasma free fraction, % free (human, rat, mouse, dog, monkey)		25, 27, 23, 44, 35		87, 87, 84, 93, 87
Caco-2, efflux ratio		1.1		2.5

[a] $n \geq 4$. [b] [^{125}I]-bungarotoxin binding. [c] Panel of nicotinic acetylcholine receptors $\alpha1\beta1\delta\varepsilon$, $\alpha3\beta4$, and $\alpha4\beta2$ [d] Panel of human CYP isozymes: 3A4-BFC, 3A4-BZR, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6. [e] 12% inhibition at 10 μM and 38% inhibition at 30 μM concentrations

Scheme 1. Synthesis of Quinuclidine Spiroimidates 1a–h[a]



[a] Reagents: (a) benzyl chloroformate, Na_2CO_3, CH_2Cl_2/H_2O (21%); (b) chiral supercritical fluid chromatography purification; (c) 3 M aqueous HCl/acetone; (d) H_2, Pd–C (69% for steps c, d); (e) NaH, CS_2, CH_3I, THF or NaOH, CS_2, CH_3I, DMF (8–77%); (f) **4**, Cs_2CO_3 (43–96%); (g) 1,1′-thiocarbonyldipyridin-2(1*H*)-one (33%); (h) **4**, Cs_2CO_3, *N*,*N*-diisopropylcarbodiimide (11%). [#] Synthesis of **5a–h** is described in the Supporting Information.

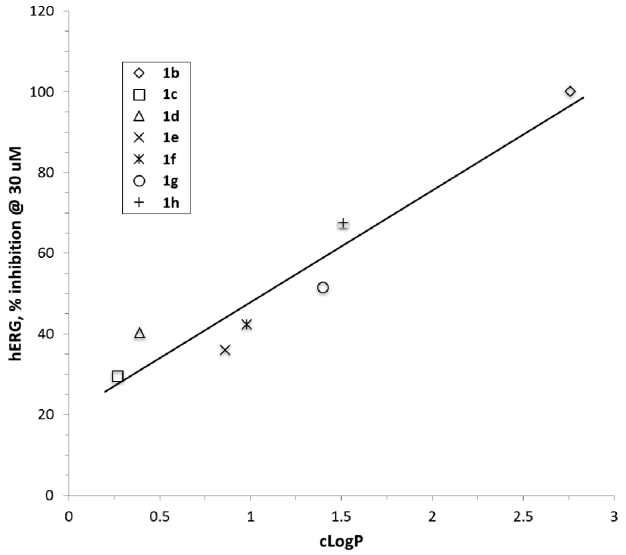


Figure 3. Relationship of hERG inhibition to cLogP values for **1b–h**. cLogP values were calculated using the LogP calculator available in the ACD/Laboratories ChemSketch software package.[37]

μM) activity at HEK293 cells expressing related rat nicotinic acetylcholine receptors ($\alpha1\beta1\delta\varepsilon$, $\alpha3\beta4$, $\alpha4\beta2$). In whole cell voltage clamp electrophysiology experiments, **1c** exhibited a potent, partial agonist profile (rat EC_{50} = 100 nM, peak Y_{max} 27%, area Y_{max} 67%; human EC_{50} = 300 nM, peak Y_{max} 24%, area Y_{max} 78%). In *in vitro* competition binding studies, **1c** potently displaced antagonist [^{125}I]-bungarotoxin (BTX) binding from recombinant rat $\alpha7$ (K_i = 3.3 nM) and human $\alpha7$ receptors (K_i = 8.1 nM). Compound **1c** demonstrated functional antagonism at 5-HT_{3A} receptors with an IC_{50} = 8.1 μM, corresponding to >300-fold selectivity versus $\alpha7$ receptor agonism. Additionally, **1c** exhibited no significant pharmacological activities in our internal screening panel of 30 other receptor and enzyme targets, which included muscarinic receptor subtypes (hM_1, hM_3, hM_4, hM_5).[42]

The effect of **1c** on episodic memory was evaluated in the mouse NOR model, our primary measure of cognitive improvement (Figure 4). This model utilizes the natural tendency of mice to spend more time exploring novel, unfamiliar objects relative to familiar objects encountered previously during the training (drug) phase of the task. Mice were treated subcutaneously (0.03–10 mg/kg, *sc*) with **1c** 30 min prior to training. Object recognition memory retention was examined 24 h later. A robust increase in novel object exploration was demonstrated at doses of 0.1–10 mg/kg, *sc*, indicative of improved object recognition memory (Figure 4). The associated average plasma exposure for **1c**, determined 30

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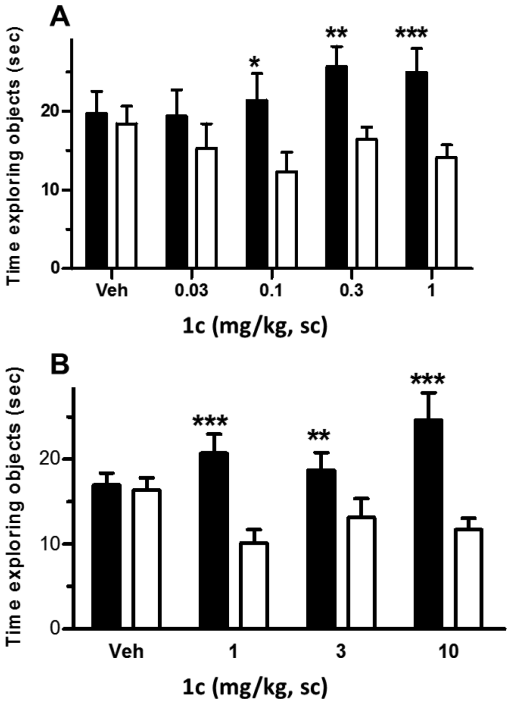

Figure 4. Effects of **1c** in mouse novel object recognition experiments. (A) Low dose experiment. (B) High dose experiment. Filled bars correspond to time of exploration of novel objects. Open bars correspond to time of exploration of familiar objects. Paired *t* tests were used to compare the statistical difference between time exploring novel and familiar objects; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

min after dosing in satellite groups of mice, was 52 nM at the minimum efficacious dose (MED), 0.1 mg/kg, *sc*.

Compound **1c** was evaluated in the hERG patch clamp assay and shown to inhibit the hERG channel 12% at 10 μM and 38% at 30 μM concentrations. Thus, the hERG IC_{50} was determined to be >30 μM, a potency at least 10-fold weaker than that of **1a** (Table 1). In order to place this parameter in the context of plasma drug levels at the MED in the NOR model, we used uncorrected plasma exposures since mouse plasma free fraction levels were very high (84%). At the MED of **1c**, 0.1 mg/kg, *sc*, the plasma exposure was >600-fold less than the hERG IC_{50}, representing a significant improvement in hERG-related cardiovascular risk compared to **1a**.

Table 2 outlines the pharmacokinetic parameters of **1c** in preclinical species. Compound **1c** demonstrated high clearance and a short $T_{1/2}$ in mouse and rat (1.1 and 0.7 h, respectively), moderate clearance and a $t_{1/2}$ of 4.4 h in cynomolgous monkeys, and moderate clearance and a $t_{1/2}$ of 5.5 h in dog. Bioavailability was good to excellent across species (45−100%).

In mice, the brain-to-plasma ratio was 0.21 at 30 min postdose (1 mg/kg). The major metabolite of **1c** was the corresponding quinuclidine *N*-oxide **7**,[42] which had greatly reduced α7 activity (EC_{50} in FLIPR assay >50 μM). Screening in ADME profiling and against a panel of 30 receptor and enzyme targets did not reveal pharmacological liabilities for this metabolite.[42]

In summary, **1c** (BMS-933043) is a potent and selective α7 nACh receptor partial agonist, which was active in a preclinical model of cognitive improvement in mice. Compound **1c** had reduced cardiovascular liability compared to earlier analogues based on reduced interaction with the hERG channel. A full description of the preclinical phamacology of compound **1c** was recently reported.[43] Based on the profile described in these reports, **1c** was advanced into Phase I clinical studies.[44]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00032.

Experimental details for synthetic procedures and associated chemical data for compounds **1**−**7**, pharmacological screening data, and biological methods (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

α7 nAChR, α7 neuronal nicotinic acetylcholine receptor; 5-HT_{3A}, 5-hydroxytryptamine 3A; ACh, acetylcholine; BTX, bungarotoxin; EP, electrophysiology; NOR, novel object recognition; FLIPR, fluorescence imaging plate reader

Table 2. Single-Dose Pharmacokinetic Parameters of 1c[42]

	mouse		rat		dog		monkey	
	iv	po	iv	po	iv	po	iv	po
dose (mg/kg)	1	10	1	10	1	5	1	5
Vss (L/kg)	7.0		2.9		5.5		5.7	
CLTp (mL/min/kg)	96		70		15		17	
C_{max} (μM)		0.55		1.6		3.2		1.3
$t_{1/2}$ (h)	1.1		0.7		5.5		4.4	
AUC (μM·h)	0.53	3.2	0.75	7.2	3.4	19	3.0	11
%F		45		97		100		70

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