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Development of 4-Heteroarylamino-1′-azaspiro[oxazole-5,3′-bicyclo[2.2.2]octanes] as α7 Nicotinic Receptor Agonists

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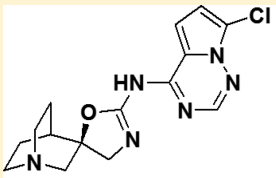
Supporting Information



21

α7 nAChR EC_{50} = 95 ± 17 nM
α7 / 5-HT_{3A} Selectivity Ratio = 310
mouse NOR MED = 0.03 mg/kg
improved selectivity relative to hERG

ABSTRACT: We describe the synthesis of quinuclidine-containing spiroimidates and their utility as α7 nicotinic acetylcholine receptor (nAChR) partial agonists. A convergent synthetic route allowed for rapid SAR investigation and provided a diverse set of fused 6,5-heteroaryl analogs. Two potent and selective α7 nAChR partial agonists, (1′*S*,3′*R*,4′*S*)-*N*-(7-bromopyrrolo[2,1-*f*][1,2,4]triazin-4-yl)-4H-1′-azaspiro[oxazole-5,3′-bicyclo[2.2.2]octan]-2-amine (**20**) and (1′*S*,3′*R*,4′*S*)-*N*-(7-chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yl)-4H-1′-azaspiro[oxazole-5,3′-bicyclo[2.2.2]octan]-2-amine (**21**), were identified. Both agonists improved cognition in a preclinical rodent model of learning and memory. Additionally, 5-HT_{3A} receptor SAR suggested the presence of a steric site that when engaged led to significant loss of affinity at that receptor.

KEYWORDS: *α7 nAChR, schizophrenia, novel object recognition, quinuclidine*

Schizophrenia is a debilitating psychiatric disorder that affects 1% of the general population. Related health care costs are estimated to be in the tens of billions of dollars in the US market alone. The chronic nature of this disease leads to a decrease in life expectancy by approximately 10 years due to a 2−3-fold increased rate of all-cause mortality.[1] Symptomatic domains associated with schizophrenia are characterized as positive, negative, or cognitive in nature. Existing therapies can effectively alleviate positive symptoms; however, therapeutic efficacy against negative and cognitive symptoms has remained a challenge. Additionally, treatment has proven difficult as a result of poor compliance due to extrapyramidal and metabolic side effects of existing medications.

Preclinical and early clinical data suggest that α7 neuronal nicotinic acetylcholine receptor (nAChR) agonists show promise as treatments of cognitive and negative symptoms in schizophrenia patients.[2−6] The α7 nAChR is a homopentameric ligand-gated ion channel that is centralized in the cortex, hippocampus, and subcortical limbic areas, which is associated with learning and memory.[7−9] The role that α7 nAChR plays in memory, sensory gating, and neuronal plasticity has inspired both knockout animal and pharmaceutical studies to probe the validity of this receptor as a target for improvements in learning and memory.[10,11] The outcomes of these studies show enhancement in animal learning and memory function, reversal of memory and sensory gating deficits, and anxiolitic properties.[12] The ability to affect biological functions such as memory and sensory gating make the α7 nAChR an attractive target for pharmaceutical manipulation, and such efforts could lead to treatments for neurological disorders such as schizophrenia and Alzheimer's disease.[13,14]

Acetylcholine structural mimics are the predominant α7 nAChR ligands described in the literature, most of which arose from AR-R17779, the first selective α7 nAChR agonist identified.[15] These molecules typically include three pharmacophoric elements: a rigid basic amine, a central polar group with a hydrogen-bond acceptor, and a lipophilic aryl/heteroaryl group attached to the central region (Figure 1).[16,17] In our previous disclosure, we described a novel series of quinuclidine-containing spirocyclic α7 nAChR partial agonists **1** built on similar principles (Figure 1).[18] In this chemotype, the quinuclidine functioned as the rigid amine, and the spiroimidate provided a centralized hydrogen-bond acceptor. Importantly, this spiroimidate series **1** provided partial agonists, which are expected to mitigate receptor desensitization associated with full agonism.[19,20] It should be noted that many earlier reported α7 nAChR agonists also act as serotonergic 5-HT_{3A} antagonists due to high sequence homology between the two recep-

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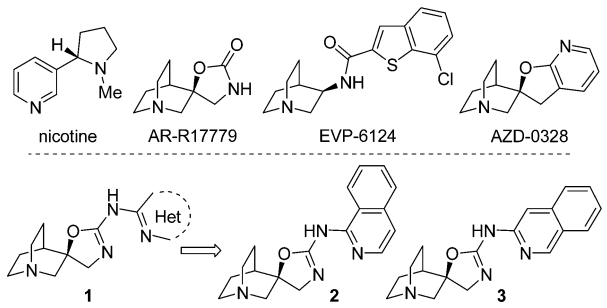


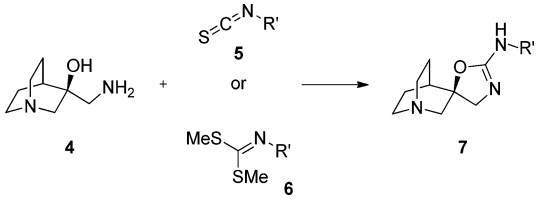
Figure 1. Examples of known α7 nAChR ligands.

tors.[21−24] Interestingly, we were previously able to build in selectivity for the α7 nAChR with heteroaryl modifications and changes to biaryl ring geometries (e.g., **2** vs **3**).[18]

We have reported that potent α7 nAChR partial agonist **3** (Figure 1) was efficacious in the novel object recognition (NOR) cognition assay: memory retention in mice was observed at 0.1, 0.3, and 1.0 mg/kg, demonstrating its central activity as an α7 nAChR agonist.[18] Certain analogs with similar concentration−response electrophysiology (EP) profiles and pharmacokinetic properties had significantly different activity profiles in behavioral assays. Translational considerations prompted additional SAR studies to improve our understanding of *in vitro* profiles and their predictive power with respect to *in vivo* models used in our preclinical progression scheme. Additionally, identification of a suitably selective molecule with an acceptable off-target profile remained challenging for the field.[13,14,16,17] For example, certain analogs demonstrated low micromolar inhibition of the hERG potassium channel, an activity associated with cardiovascular liabilities.

Herein we report heteroaryl modifications to **1** that improve selectivity over 5-HT_{3A} antagonism and reduce potency at the hERG channel, thus mitigating hERG-related cardiovascular risks. Outside of preliminary work focused on establishing the minimum pharmacophore, our previous efforts were largely confined to unsubstituted 6,6-fused biaryls.[18] In this study we prepared 6,5-fused systems with varying substitution patterns to further probe the hypothesized lipophilic pocket of the α7 nAChR. New spiroimidates were readily synthesized in enantiopure form using an established route (Scheme 1).

Scheme 1. Synthetic Route to Spiroimidates 7



This protocol involved coupling and requisite cyclization of amino alcohol **4** with a structurally diverse set of isothiocyanates **5** and imidodithioates **6** to provide spiroimidate products **7**.

We screened for both α7 nAChR agonism and 5-HT_{3A} antagonism in Ca^{2+}-based FLIPR (fluorescence image plate reader) assays.[18,25,26] The relationship between these two values is reported for each compound as the FLIPR selectivity ratio. Pyridine-, diazine-, and triazine-derived 6,5-fused bicycles provided highly variable levels of α7 nAChR potency and selectivity over 5-HT_{3A} that appear to be independent of ring geometry (Table 1). Specifically, unsubstituted heteroaryls provided minimal selectivity over 5-HT_{3A} inhibition (representative compounds **10**−**12**, **14**, **16**); however, the addition of simple substituents often led to dramatic changes in potency at the 5-HT_{3A} receptor. For example, *N*-methylation of 7H-pyrrolo[2,3-*d*]pyrimidine afforded highly selective spiroimidate **13**, whereas similar unsubstituted analogs **10**−**12** were unselective. This promising result suggested that the equivalent elaboration of other fused 6,5-heteroaryls with the same ring geometry could result in higher selectivity.

Subsequent SAR efforts expanded into 6,5-fused heteroaryl groups with bridgehead nitrogen atoms (Table 1, compounds **14**−**20**). Pyrrolo[1,2-*a*]pyrazine **16** was very potent in the α7 nAChR FLIPR assay, but was a potent 5-HT_{3A} antagonist as well. Considering the increased selectivity we observed with 7-methyl-7H-pyrrolo[2,3-*d*]pyrimidine **13**, 6-bromopyrrolo[1,2-*a*]pyrazine **17** was prepared. Notably, installation of the C6 bromide provided a greater than 400-fold selectivity improvement over the parent pyrrolo[1,2-*a*]pyrazine **16** via diminution of the 5-HT_{3A} receptor affinity. Methylation at C3 of the pyrrolo[1,2-*a*]pyrazine ring led to the opposite result (e.g., 3-methylpyrrolo[1,2-*a*]pyrazine **18**). Subsequent synthesis of pyrrolo[2,1-*f*][1,2,4]triazines **19** and **20** provided spiroimidates with equipotent activity at the α7 nAChR. Importantly, the 5-HT_{3A} receptor SAR trend was consistent with similar heteroaryls and suggested there was a steric site in the 5-HT_{3A} receptor that when engaged led to significant loss of affinity at that receptor (e.g., the 7-bromopyrrolo[2,1-*f*][1,2,4]-triazine **20** demonstrated a selectivity boost of more than 900-fold over the des-bromo analog **19**).

After weighing factors such as potential for selectivity against 5-HT_{3A}, α7 nAChR potency, and metabolic stability,[27] the pyrrolo[2,1-*f*][1,2,4]triazine bicycle was chosen for further SAR studies. Several analogs were prepared in order to probe the effects of substitution on potency and selectivity (**21**−**27**). Relative to unsubstituted analog **19**, chlorination and fluorination at C7 led to losses in potency and selectivity that, in conjunction with data generated for the bromo analog **20**, appear to trend with substituent volume (compounds **21**−**23**). C7 methylation led to high potency and selectivity (**23**). A C7 cyano substituent (**24**) was also reasonably potent, fitting with the observation that large substituents at C7 were more potent than smaller substituents. Bromination at C6 and C5 provided analogs **25** and **26** and led to an increase in 5-HT_{3A} receptor potency with a greater than 42-fold loss in selectivity over 5-HT_{3A} receptor antagonism (vs C7-bromo analog **20**). The potency/selectivity profile of 5,7-dibromopyrrolo[2,1-*f*][1,2,4]triazine **27** was also less attractive than monosubstituted compounds **20**, **21**, and **23**.

Select examples of pyrrolo[2,1-*f*][1,2,4]triazine derivatives with attractive α7 nAChR FLIPR profiles were progressed to electrophysiology studies. Analogs were evaluated for potency and efficacy (Y_{max}), as measured by patch clamp using HEK-293 cells that express rat α7 nAChR.[27] Compounds **20** and **21** were the two most potent pyrrolo[2,1-*f*][1,2,4]triazine-containing analogs with selectivity over 5-HT_{3A} (280 nM and 400 nM, respectively). The area and peak Y_{max} values were consistent with partial agonism (area/peak: 62%/26% and 73%/28%, respectively).[28]

The quinuclidine-containing spiroimidate core was shown to be optimal in earlier series.[18] In order to confirm these observations, several modifications were made to the spirocycle with 7-chloropyrrolo-[2,1-*f*][1,2,4]triazine (Table 2). This

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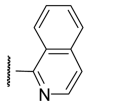
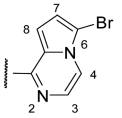
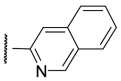
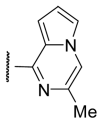
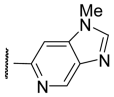
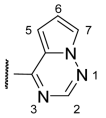
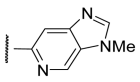
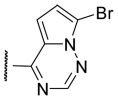
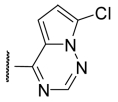
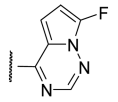
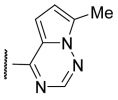
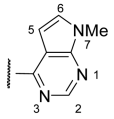
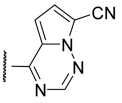
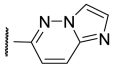
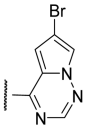
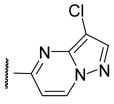
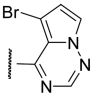
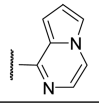
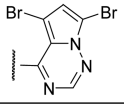
Table 1. α7 nAChR and 5-HT$_{3A}$ FLIPR Data for Various Heteroaryl-Containing Spiroimidates

	α7 EC_{50} ± SEM (nM)[a]	5-HT_{3A} IC_{50} ± SEM (nM)[a]	Selectiv. Ratio[b]		α7 EC_{50} ± SEM (nM)[a]	5-HT_{3A} IC_{50} ± SEM (nM)[a]	Selectiv. Ratio[b]
 **2**[18]	210 ± 70 (4)[18]	1,600 ± 700 (4)	7.5	 **17**	91 ± 45 (2)	12,000 ± 1,000 (2)	130
 **3**[18]	9 ± 5 (29)[18]	480 ± 160 (29)	52	 **18**	940 ± 160 (2)	7 ± 1 (2)	0.0074
 **8**	70 ± 10 (2)	4,200 ± 700(2)	60	 **19**	41 ± 8 (3)	35 ± 9 (2)	0.85
 **9**	4,200 ± 100 (2)	4,000 ± 300 (2)	0.95	 **20**	45 ± 11 (12)	34,000 ± 8,000 (8)	760
 **10**	63 (1)	54 (1)	0.86	 **21**	95 ± 17 (25)	29,000 ± 3,000 (12)	310
 **11**	410 ± 100 (4)	690 (1)	1.7	 **22**	260 ± 50 (7)	320 ± 50 (3)	1.2
 **12**	40 ± 11 (3)	50 ± 4 (2)	1.3	 **23**	41 ± 10 (4)	71,000 ± 5,000 (3)	1,700
 **13**	31 ± 4 (5)	86,000 ± 14,000 (2)	2,800	 **24**	140 ± 2 (4)	19,000 ± 1,000 (4)	140
 **14**	100 ± 40 (2)	250 ± 30 (2)	2.5	 **25**	250 ± 80 (3)	2,200 ± 500 (4)	8.8
 **15**	260 ± 70 (4)	7 ± 1 (4)	0.027	 **26**	320 ± 80 (4)	5,600 ± 700 (4)	18
 **16**	18 ± 3 (2)	5 (2)	0.28	 **27**	120 ± 30 (4)	28,000 ± 3,000 (4)	230

[a]Number of determinations in parentheses. [b]Ratio = 5-HT_{3A} IC_{50}/α7 EC_{50}.

fused heterocycle was chosen because of its superior overall profile, including α7 nAChR selectivity, EP potency, and hERG profile (data not shown). The S-enantiomer **28** of spiroimidate **21** was prepared and exhibited only a slight loss in α7 nAChR potency and 5-HT_{3A} selectivity.[18] Target potency dropped considerably when the imidate heteroatoms were exchanged (compound **29**). Homologation of the imidate core provided spirocycle **30**, which was considerably weaker and failed to offer any improvement over lead spiroimidate **21**.[18] Lastly, 2.2.1-bicyclic amine analog **31**[29] was prepared, but was found to be nonselective and provided no advantage over the quinuclidine moiety.

Partial agonists **20** and **21** were chosen to advance into *in vivo* efficacy models because of excellent selectivity and reasonable potency in the FLIPR assays. We used the mouse NOR behavioral assay that measures visual recognition memory, which is an impaired cognitive domain in schizophrenia patients.[30] In this experiment, both drug-treated and control mice are shown two identical objects followed by a 24 h delay, a time sufficient for natural forgetting. Upon reintroduction of a familiar object with a novel object, improved memory can be measured as time spent exploring the novel object due to the innate tendency of mice to explore unfamiliar objects. Both halo analogs (**20** and **21**) led to significantly increased time spent exploring the novel object over the familiar object. 7-Bromopyrrolo[2,1-*f*][1,2,4]triazine **20** was active ($p < 0.05$) with an MED = 0.01 mg/kg and plasma concentration = 7 nM (B/P = 4.9, Figure 2). 7-

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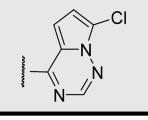
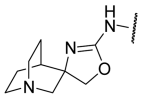
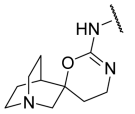
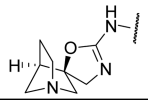
Table 2. α7 nAChR and 5-HT$_{3A}$ FLIPR Data for 7-Chloropyrrolo-[2,1-*f*][1,2,4]triazine Analogs

		α7 EC_{50} ± SEM (nM)[a]	5-HT_{3A} IC_{50} ± SEM (nM)[a]	Selectiv. Ratio[d]
	**28**	300 ± 60 (4)	87,000 ± 8,000 (2)	290
	**29**[b]	5,600 ± 1,200 (4)	170 ± 4 (3)	0.030
	**30**[b]	1,100 ± 100 (4)	61,000 ± 8,000 (3)	55
	**31**[c]	180 ± 30 (2)	180 ± 50 (2)	1.0

[a]Number of determinations in parentheses. [b]Racemic mixture. [c]des-Chloro analog. [d]Ratio = 5-HT_{3A} IC_{50}/α7 EC_{50}.

Chloropyrrolo[2,1-*f*][1,2,4]triazine **21** was similarly active ($p < 0.01$), with an MED = 0.03 mg/kg and plasma concentration = 18 nM (B/P = 1.9, Figure 2).

Both leads **20** and **21** were evaluated in the hERG patch clamp assay to measure for potential cardiovascular toxicity.[18] 7-Bromopyrrolo[2,1-*f*][1,2,4]triazine **20** (hERG IC_{50} = 2.5 μM) and 7-chloropyrrolo[2,1-*f*][1,2,4]triazine **21** (42% hERG inhibition at 3.0 μM) were considered in the context of plasma drug levels at respective MEDs. Since mouse plasma free fraction levels were very high (50−75%), uncorrected plasma exposures were used to calculate hERG margins. Plasma exposures at the MED of bromo **20** and chloro **21** were 400-fold and 170-fold[31] lower, respectively, than the hERG IC_{50} values.

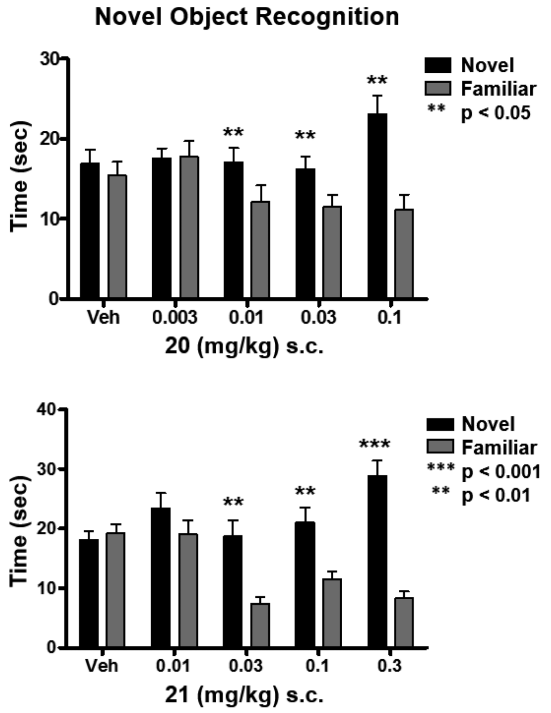


Figure 2. Pretreatment with 0.01−0.1 mg/kg spiroimidate **20** or 0.03−0.3 mg/kg spiroimidate **21** 30 min prior to training significantly increased the time spent exploring the novel object compared to the familiar object when tested 24 h later.[27]

In summary, 6,5-fused bicyclic heteroaryls were appended to a quinuclidine-containing spiroimidate core to provide novel, potent α7 nAChR partial agonists. In the course of these studies, we discovered a very steep SAR for 5-HT_{3A} receptor affinity driven by rigid steric interactions. The pyrrolo[2,1-*f*][1,2,4]triazine moiety emerged as a leading candidate for additional elaboration due to attractive α7 nAChR FLIPR potency and potential for increasing selectivity over 5-HT_{3A} antagonism. Pyrrolo[2,1-*f*][1,2,4]triazines **20** and **21** significantly improved memory retention in the NOR behavioral model and were evaluated in a hERG patch clamp assay. These results warranted follow-up *in vivo* studies, the results of which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00471.

Experimental procedures and characterization data for key compounds, and details of *in vitro* and *in vivo* assays (PDF)

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Notes

The authors declare no competing financial interest.

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