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Discovery of *N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]furo-[2,3-*c*]pyridine-5-carboxamide as an agonist of the α7 nicotinic acetylcholine receptor: In vitro and in vivo activity

Brad A. Acker, E. Jon Jacobsen, Bruce N. Rogers, Donn G. Wishka, Steven C. Reitz, David W. Piotrowski, Jason K. Myers, Mark L. Wolfe, Vincent E. Groppi, Bruce A. Thornburgh, Paula M. Tinholt, Rodney R. Walters, Barbara A. Olson, Laura Fitzgerald, Brian A. Staton, Thomas J. Raub, Michael Krause, Kai S. Li, William E. Hoffmann, Mihaly Hajos, Raymond S. Hurst and Daniel P. Walker*

Neuroscience Research, Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, USA

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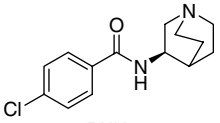
Abstract—A novel α7 nAChR agonist, *N*-[(3*R*,5*R*)-1-azabicyclo[3.2.1]oct-3-yl]furo[2,3-*c*]pyridine-5-carboxamide (**3a**, PHA-709829), has been identified for the potential treatment of cognitive deficits in schizophrenia. The compound shows potent and selective α7 in vitro activity, excellent brain penetration, good rat oral bioavailability and robust in vivo efficacy in a rat auditory sensory gating model.

Due in large part to the significant unmet medical need for treating the cognitive deficits in schizophrenia,[1] the α7 nicotinic acetylcholine receptor (nAChR) has emerged as a pharmacological target of considerable interest in neuroscience research.[2] Physiological,[3] pharmacological,[4] and human genetic studies[5] have strongly established the α7 nAChR as a viable target for treating the cognitive deficits of schizophrenia. Several α7 nAChR agonists have recently entered human clinical trials,[6] and the search for novel ligands with improved safety profiles is desirable.

As part of an on-going α7 nAChR drug discovery program, we have been interested in the synthesis and biological profiling of novel azabicyclic aryl amides as α7 nAChR agonists.[7] Our program objective was to identify novel, potent and orally bioavailable α7 nAChR agonists with an equal or better in vitro and in vivo profile to that of PHA-543613.[7b] Recently, we disclosed the synthesis of (3*R*,5*R*)-1-azabicyclo[3.2.1]octane-3-amine dihydrochloride (**1**) and demonstrated that the corresponding *para*-chlorophenyl benzamide **2** possesses equal activity in the α7-5HT$_3$ chimera assay to the potent α7 nAChR agonist, PNU-282987.[8] Herein we detail the synthesis, SAR and in vivo activity of an expanded set of amides derived from amine **1**.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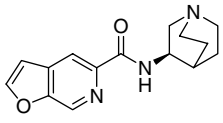
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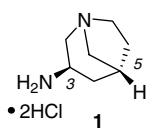
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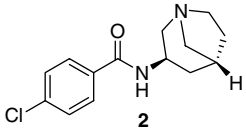
2

Amides of type **3** were prepared in a single step by HATU-mediated coupling of enantiomerically pure amine **1** with various aryl carboxylic acids (Scheme 1).[8] The custom aryl carboxylic acids utilized in this study were either available from a commercial vendor or prepared according to literature procedures.[7b,c] Prior

Keywords: Azabicyclic; α7; Nicotinic; nAChR; Schizophrenia; PHA-543613; PHA-709829.
* Corresponding author. Tel.: +1 636 247 1192; fax: +1 636 247 2086; e-mail: daniel.p.walker@pfizer.com

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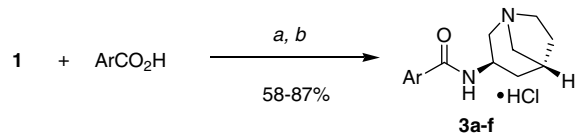


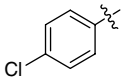
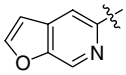
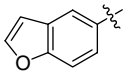
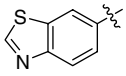
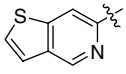
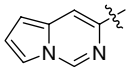
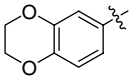
Scheme 1. General synthetic route for the preparation of type **3** amides. Reagents and conditions: (a) HATU, *i*-Pr_2NEt, DMF, 0° → rt, 24 h; (b) HCl, MeOH.

SAR studies by our lab had established that there is good modularity between the azabicyclic amine and the aryl fragment within this class of compounds.[7c] Hence, the primary interest of this study was to prepare and profile amide **3a**, which possesses the same furopyridine heterocycle found in our earlier clinical candidate, PHA-543613. However, to ensure that we did not overlook any fortuitous benefits of amine **1**, we prepared a variety of other type **3** amides possessing aryl carboxylic acids that showed promising in vitro activity in the corresponding quinuclidine series.

Newly prepared compounds, along with α7-5HT_3 chimera functional potency, α7 nAChR K_i and stability in rat liver microsomes (RLM), are detailed in Table 1; PHA-543613, PNU-282987, and chlorobenzamide **2** are shown for comparative purposes. We were pleased to see that furopyridine **3a**,[9] which is structurally the most similar analog in Table 1 to that of PHA-543613, shows very similar activity in the α7-5HT_3 chimera functional assay and similar affinity in the α7 binding assay. Compound **3a** also shows comparable stability in RLM to that of PHA-543613. With the exception of benzodioxane **3f**, which did not meet our potency criteria in the functional assay, all the remaining compounds in Table 1 show similar binding and functional activity to that of PHA-543613. This was not unexpected given the potent α7 activity displayed by these heterocycles in the corresponding quinuclidine amide series.[7b,c] Because our primary in vivo efficacy studies were performed in rat (vide infra), achieving reasonable stability in RLM was an important aspect of our screening funnel. Thus, thienopyridine **3d** and pyrrolopyrimidine **3e** were removed from further consideration due to their low stability in RLM.

Compounds **3a**–**3c** were profiled in a brain delivery assessment (BDA) screen, which measures a compound's ability to penetrate the blood–brain barrier (BBB) (Table 2).[10] The screen consists of three assays, a mouse brain uptake assay (MBUA), a Maden Darby Canine Kidney (MDCK) cell permeability assay and a multidrug resistant (MDR) P-glycoprotein (Pgp) assay. Furopyridine **3a** shows excellent CNS penetration in the BDA screen, displaying a profile very similar to PHA-543613. Benzofuran **3b** shows reasonable BBB penetration in this model; however, the compound also shows brain accumulation. Given the α7 nAChR's

Table 1. 3-Amino-1-azabicyclo[3.2.1]octane aryl amides

Compound	Ar	α7-5HT_3 chimera EC_{50}[a] (nM)	α7 K_i[b] (nM)	In vitro RLM[c] Eh
PHA-543613		65 ± 11 (n = 11)	9.0 ± 1.0 (n = 13)	0.56
PNU-282987		128 ± 31 (n = 16)	24 ± 8 (n = 13)	<0.27
2		190, 350	18, 26	0.37
3a		46	2.9, 3.9	0.51
3b		81	6.2, 4.7	<0.27
3c		182	21, 28	<0.27
3d		70	7.0, 6.1	0.71
3e		129	14, 15	0.86
3f		430	29, 32	0.74

[a] Cell-based FLIPR assay using SH-EP1 cells expressing the α7-5HT_3 chimera. Numbers indicate EC_{50} values generated from individual 7-point concentration–response relationships in triplicate; when >3 measurements were made, mean ± SEM is reported.

[b] [^{3}H]MLA rat brain homogenate binding assay. Numbers indicate individual K_i values; when >3 measurements were made, mean ± SEM is reported.

[c] RLM, rat liver microsomes; in vitro compound stability (Eh) is reported as the fraction of compound remaining after 30 min. as compared with the concentration at t_0.

Table 2. BDA for compounds **3a**–**3c**

Compound	MDCK (A > B)[a] $P_{app} \times 10^{-6}$ cm/s	MBUA[b] brain/plasma at 5, 60 min	Pgp[c] substrate
PHA-543613	34	1.5, 1.5	No
3a	21	1.52, 1.88	No
3b	3.8	0.27, 1.15	No
3c	0.2	0.02, 0.33	Yes

[a] Madin Darby canine kidney cell permeability assay, apical to basel (A > B) permeability expressed as P_{app}.
[b] MBUA, mouse brain uptake assay, brain to plasma = concentration in brain divided by concentration in plasma following a 10 mg/kg dose.
[c] Assessment based on compound's performance in a multidrug-resistant P-glycoprotein assay. Compounds possessing efflux ratios (B > A)/(A > B) >3 were labeled as Pgp substrates.

known desensitization profile,[11] brain accumulation was not a desirable attribute. Benzothiazole **3c** shows limited brain penetration, which is likely due to the fact that the compound shows significant efflux in the MDR Pgp assay. Based on these data, **3a** clearly emerged as the best compound among this small group of related azabicyclic amides.

Compound **3a** was evaluated in a set of ligand-gated ion channel selectivity screens, including the 5-hydroxytrypamine 3 (5-HT_3) receptor, the predominant ganglionic nAChR ($\alpha3\beta4$), the neuromuscular nAChR ($\alpha1\beta1\lambda\delta$), and the $\alpha4\beta2$ nAChR (Table 3). Compound **3a** shows high selectivity against all these receptors except 5-HT_3, where the selectivity was ca. 100-fold. Further work demonstrated that compound **3a** is a weak 5-HT_3 antagonist. This weak off-target activity was expected to carry minimal risk based on clinical data for the potent 5-HT_3 receptor antagonist Ondensetron.[13] Compound **3a** shows minimal cross reactivity against a panel of human muscarinic receptors M1, M2, and M3.[14] Finally, the affinity of furopyridine **3a** for the human. $\alpha7$ nAChR is very similar to the rat $\alpha7$ nAChR, which was not unexpected given the 94% amino acid sequence identity between rat and human $\alpha7$ nAChR subunits.[15]

In vitro cardiovascular safety was assessed in a patch-clamp hERG K^+ channel assay (Table 3).[16] Compound **3a** shows 25% inhibition of the hERG channel at a concentration of 20 μM.[17] This level of inhibition was very encouraging as it is comparable to that observed for PHA-543613 (29% at 20 μM).[7b] In order to further understand the cardiovascular profile of **3a** and establish a therapeutic index (TI), an in vivo cardiovascular safety study was performed using an acute dog ECG model. The 'No observable adverse effects level' or NOAEL for **3a** was established at a dose of 40 mg/kg (C_{max} = 22 μM), which is fivefold higher than the NOAEL for PHA-543613 (C_{max} = 3.8 μM).

Furopyridine **3a** is expected to possess low plasma protein binding (PPB) based on the measured PPB value for PHA-543613 and its similarity in structure and log *D* to that of PHA-543613 (Table 4). Compound **3a** shows improved stability in human liver microsomes compared to rat. This was not unexpected given that the same trend was seen for other azabicyclic amides, including PHA-543613; however, the data do suggest that RLM is potentially underestimating compound stability in humans for this class of compounds.

Table 3. In vitro selectivity screens and hERG data

Compound	Rat 5-HT_3 K_i (nM)	Nicotinic selectivity data			Human M1, M2, M3[e] % inhib	hERG[f] % inhib	Human $\alpha7$ K_i[g] (nM)
		$\alpha3\beta4$[a,b] IC_{50} (μM)	$\alpha1\beta1\gamma\delta$ [a,c] IC_{50} (μM)	$\alpha4\beta2$[d] % inhib			
PHA-543613	630	>100	>100	13	16, 23, 33	29	7
3a	350	>100	>100	<1	16, 25, 15	25	9

[a] FLIPR cell-based functional assay; numbers indicate EC_{50} values generated from individual 7-point concentration–response relationships.
[b] SH-SY5Y cells expressing $\alpha3\beta4$.
[c] TE671 cells, native $\alpha1\beta1\gamma\delta$.
[d] Rat brain homogenate binding assay, [^{3}H]cytosine, % block at 1 μM.
[e] Human muscarinic receptor in transfected CHO cells using [^{3}H]pirenzepine (M1), [^{3}H]AF-DX 384 (M2) or [^{3}H]DAMP (M3) as a radio ligand, %block at 10 μM.
[f] In vitro effect on hERG current (IKr), HEK cells expressed as percent inhibition at a concentration of 20 μM.
[g] IMR32 human cells, [^{3}H]MLA.

Table 4. ADME and pharmacokinetic data

Compound	Human PPB[a] f_u	HLM[c] Eh	HLM $t_{1/2}$ (min)	Rat in vivo pharmacokinetic properties[d]			
				CL (ml/min/kg)	Half-life (min)	V_{ss} (L/kg)	%*F*
PHA-543613	0.83 ± 0.041	<0.26	>120	33 ± 5	36 ± 6.0	1.8 ± 0.2	65 ± 23
3a	Est. 0.75–0.85[b]	<0.26	>120	72 ± 25	48 ± 0.0	2.4 ± 0.3	40 ± 16

[a] In vivo human plasma protein binding, expressed as fraction unbound (f_u), determined at a drug concentration of 0.100 μg/mL.
[b] Estimation based on similar log *D* and structure to PHA-543613.
[c] HLM, human liver microsomes; in vitro extraction ratios (Eh) are reported as the fraction of compound remaining as compared with the concentration at t_0.
[d] Pharmacokinetic data generated following a single 5.0 mg/kg dose (Ref. 12) in Sprague–Dawley rats.

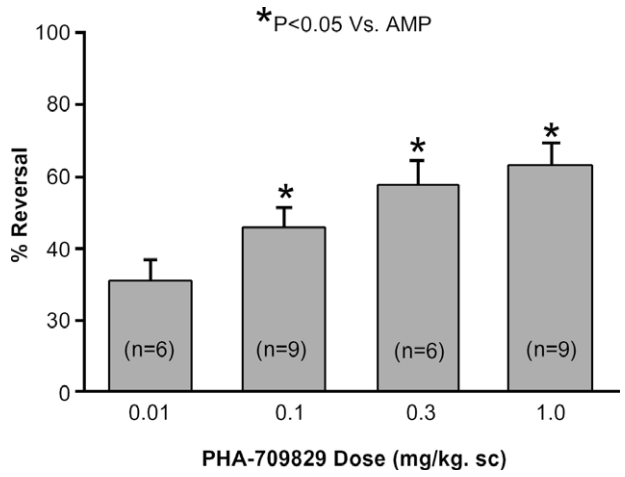


Figure 1. Effect of compound **3a** (PHA-709829) (0.01–1.0 mg/kg) on the auditory gating deficit in amphetamine treated rats.[22,19] Auditory gating was measured as the ratio of 'conditioning' and 'test' field potentials (EEG) evoked by paired auditory tones delivered at 0.5 Hz. Subsequent to disrupting the normal auditory gating with amphetamine (1 mg/kg, iv), PHA-709829 (sc) was administered and gating was monitored for 30 min. Results are expressed as a % Reversal of the amphetamine-induced deficit.

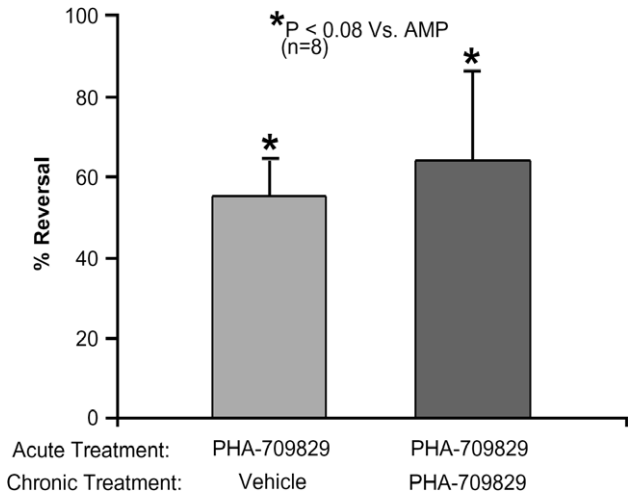


Figure 2. Chronic dosing studies of PHA-709829: Vehicle (0.9% saline, sc, $n = 8$) or PHA-709829 (1 mg/kg, sc, $n = 8$) administered twice daily for 6 days. PHA-709829 (1 mg/kg, sc) was tested for the ability to reverse the amphetamine-induced gating deficit on the seventh day.

The pharmacokinetics of compound **3a** were determined in rat following a single oral dose administration of the compound (Table 4). The clearance (CL) of compound **3a** is higher than that of PHA-543613, which was not predicted by the RLM stability assay. However, compound **3a** has a longer half-life than PHA-543613, which is attributed to the compound's higher volume of distribution. Also, the higher in vivo rat clearance of **3a** was less concerning based on its high in vitro stability in HLM. The bioavailability for **3a** was somewhat lower than for PHA-543613 but still within an acceptable range.

The in vivo pharmacological activity of compound **3a** (PHA-709829) was tested in a rat model of impaired auditory gating.[18] It has been shown previously that amphetamine-induced auditory gating deficit in rats is restored by nicotine, and partial or full α7 nAChR agonists, including PNU-282987 and PHA-543,613.[18,19,7b] In the present study, a dose-dependent, significant reversal of amphetamine-induced gating deficit by PHA-709829 (0.01–1.0 mg/kg, sc, $n = 6$–9)[12] was demonstrated (Fig. 1). The minimum effective dose was 0.1 mg/kg (sc, $n = 9$), which resulted in a 60 ± 4.3 nM, and a 47 ± 4 nM plasma and brain exposure, respectively, determined at 37 ± 3 min after drug administration. The minimum effective dose for PHA-543613 in the same assay was 0.24 mg/kg (IV, $n = 6$),[20] which resulted in a plasma concentration of 130 ± 38 nM at 30 min. Thus, PHA-709829 is twofold more potent in this assay than PHA-543613, which is consistent with the lower rat K_i of PHA-709829 (3.4 nM) versus PHA-543613 (9.0 nM).[21] The highest tested effective dose, 1 mg/kg (sc, $n = 7$) for PHA-709829 resulted in significantly higher brain (1200 ± 300 nM) and plasma (1100 ± 110 nM) exposures, while the highest ineffective dose (0.01 mg/kg, sc, $n = 6$) reached only low exposures both in brain (5.3 ± 0.3 nM) and in plasma (12 ± 3.6 nM). Brain/plasma ratios varied from 0.81 ± 0.09 to 2.7 ± 0.51 in these auditory gating in vivo electrophysiological experiments.

The ability of PHA-709829 to reverse amphetamine-induced gating deficit was also demonstrated after its repeated administration (Fig. 2). In these studies, PHA-709829 (1 mg/kg, $n = 8$) or vehicle (0.9% saline, $n = 8$) was administered subcutaneously twice a day for six days, then PHA-709829 was tested for the ability to reverse the amphetamine-induced gating deficit on the seventh day. Thus, administration of PHA-709829 (1 mg/kg, sc) on the seventh day reversed the gating deficit induced by amphetamine in both vehicle and PHA-709829 treated rats with the same potency. Acute administration of PHA-709829 resulted in very similar brain and plasma exposures in rats chronically treated with vehicle (brain: 350 ± 48 nM, plasma: 550 ± 48 nM) and PHA-709829 (brain: 350 ± 36 nM, plasma: 490 ± 45 nM). Thus, chronic administration of PHA-709829 does not affect its ability to reverse amphetamine-induced auditory gating deficits when given acutely.

In summary, several aryl amides derived from azabicyclic amine **1** were prepared as α7 nAChR agonists. In general these compounds show potent α7 activity in both the functional and binding assays, suggesting that amine **1** is an effective isostere of (3*R*)-3-amino-quinuclidine for this receptor subtype. Furopyridine **3a** (PHA-709829), possessing the same aryl fragment as our earlier clinical candidate, PHA-543613, demonstrated the best overall profile among type **3** analogs. Compound **3a** is a potent α7 nAChR agonist with good to excellent selectivity against a variety of related CNS receptors. The compound exhibits excellent CNS penetration and good oral bioavailability in a rat pharmacokinetic model. In a dog ECG cardiovascular model, the NOAEL for PHA-709829 was established at a dose fivefold higher than that of PHA-543613. In vivo efficacy profiling in an

amphetamine-induced gating model demonstrated that PHA-709829 is twofold more potent than PHA-543613, and it is efficacious over a range of doses (0.1–1.0 mg/kg). Taken together, the efficacy and safety data represent a 10-fold improvement in cardiovascular TI for PHA-709829 compared to PHA-543613. Additionally, it was shown that PHA-709829 remains efficacious after chronic administration. Future plans include profiling PHA-709829 in additional safety-related models, which could identify other advantages relative to PHA-543613.

Acknowledgments

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