N-[5-(5-Fluoropyridin-3-yl)-1H-pyrazol-3-yl]-4-piperidin-1-ylbutyramide (SEN78702, WYE-308775): A Medicinal Chemistry Effort toward an α7 Nicotinic Acetylcholine Receptor Agonist Preclinical Candidate

Riccardo Zanaletti,*,[†] Laura Bettinetti,[†] Cristiana Castaldo,[†] Ilaria Ceccarelli,[†] Giuseppe Cocconcelli,[†] Thomas A. Comery,[‡] John Dunlop,[‡] Eva Genesio,[†] Chiara Ghiron,[†] Simon N. Haydar,[‡] Flora Jow,[‡] Laura Maccari,[†] Iolanda Micco,[†] Arianna Nencini,[†] Carmela Pratelli,[†] Carla Scali,[†] Elisa Turlizzi,[†] and Michela Valacchi[†]

[†]Siena Biotech SpA, Strada del Petriccio e Belriguardo 35, 53100 Siena, Italy
[‡]Neuroscience Research Unit, Pfizer, Eastern Point Road, Groton, Connecticut 06340, United States

Ⓢ Supporting Information

ABSTRACT: α7 nicotinic acetylcholine receptors (α7 nAChR) represent promising therapeutic candidates for the treatment of cognitive impairment associated with Alzheimer's disease (AD) and schizophrenia. A medicinal chemistry effort around previously reported compound **1** (SEN15924, WAY-361789) led to the identification of **12** (SEN78702, WYE-308775) a potent and selective full agonist of the α7 nAChR that demonstrated improved plasma stability, brain levels, and efficacy in behavioral cognition models.

■ INTRODUCTION

Neuronal nicotinic acetylcholine receptors are a family of ligand gated ion channels that participate in many physiological functions. They are distributed in the central and peripheral nervous system and are permeable to cations such as Na^+, K^+, and Ca^{2+}. These receptors are combinations of five subunits that can assemble as homopentamers or heteropentamers of 12 distinct subunits (α2−α10, β2−β4). They share a common basic structure but have specific pharmacological and functional properties due to the different subunit combinations. Changes in their number and/or function are associated with a number of pathophysiological conditions.[1−3]

The homomeric α7 nAChR is one of the most abundant nicotinic receptors in the human brain and is highly expressed in regions associated with learning and memory such as the cerebral cortex and the hippocampus.[4] Experimental evidence supports the involvement of the α7 neuronal nAChR in schizophrenia and Alzheimer's disease.[5,6] Schizophrenia is characterized by positive (hallucinations, delusions) and negative symptoms (reduced affect, social withdrawal, low motivation, disorganized thoughts) and cognitive impairment (decreased attention, memory deficits). While positive symptoms are partially managed with current medications, cognitive deficits and negative symptoms still remain an unmet medical need. Cognitive impairment is an important hallmark of Alzheimer's disease as well. Modulators of the α7 nAChR have extensively been studied for the treatment of cognitive deficits in schizophrenia and AD.[7−9]

In the past decade there has been a continuing effort to develop new α7 nAChR agonists with better properties, and many of them have advanced into clinical trials. An alternative approach is the use of positive allosteric modulators (PAMs), which enhance the effect elicited by the endogenous ligand without directly activating or desensitizing the target receptor.[10]

Concerning the discovery and development of novel α7 nAChR agonists, we have previously reported **1** (SEN15924, WAY-361789, Table 1). This exhibited a promising profile, efficacy in rodent cognition models but limited plasma stability and brain exposure.[11] We describe herein the chemical exploration around this compound aimed at improving these properties.

Table 1. Effect of Chain Length on Activity
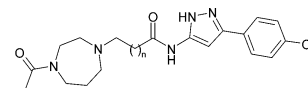
compd	n	ClogP	MW	rotatable bonds	α7 pEC$_{50}$ ± SEM (n)[a]
1	3	1.9	413.5	8	6.90 ± 0.02 (28)
2	1	1.7	385.5	6	5.07 ± 0.11 (2)
3	2	1.4	399.5	7	6.04 ± 0.04 (2)
4	4	2.4	427.5	9	5.92 ± 0.11 (2)

[a]All functional activities were measured in a calcium flux assay. Data were averaged from multiple experiments (n). All the reported compounds gave E_{max} > 90% of nicotine and were considered to be full agonists. Nicotine under the same conditions had pEC$_{50}$ = 5.97 ± 0.01, E_{max} = 102% ± 1.3 (n = 62).

■ RESULTS AND DISCUSSIONS

The initial focus of the present study was the exploration of carbon chain (CC) length to establish the most favorable distance between two pharmacophoric points, typical of our series: the basic center and the amide group (Figure 1).
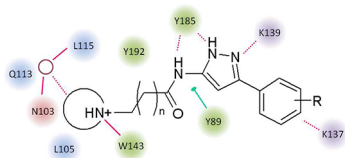

Figure 1. 2D interaction map of our series from docking studies into α7 homology model: green, hydrophobic residues; purple, positively charged residues; blue, polar residues; red, negatively charged residue; dotted lines, H-bond with amino acid side chain; pink solid lines, H-bond with amino acid backbone; green solid line, stacking interaction; red empty circle, water molecule.

According to our docking studies into a homology model for the human α7 receptor,[11] the basic center is involved in the well-known interaction with the backbone carbonyl of W143 while the amide−pyrazole system is prone to give hydrogen bonding contacts to Y185. The CC acts as a spacer between these two and is therefore expected to play a significant role in modulating receptor activity.

Starting from **1**[11] (Table 1), we noticed that a reduction of two methylene units of the chain length resulted in less active **2**. It is lacking the required distance to allow the basic nitrogen and the amide−pyrazole system to engage the pharmacophoric interactions with the protein. On the contrary, the reduction and the elongation by one methylene unit of the carbon chain length were well tolerated and led to similarly active **3** and **4**.

Since it is commonly accepted that a high molecular weight and a high number of rotatable bonds could unfavorably affect the brain permeability,[12] we opted for the 3CC analogue **3** as the initial tool for further SAR studies.

We then moved to the exploration of the region bearing the basic center in **3**. A representative set of the molecules synthesized is shown in Table 2 with their α7 activity and selectivity over homologous receptor subtypes (α1, α3, and 5HT3). We previously noted for our series that as long as the pK_a is sufficient to have the basic nitrogen protonated at physiological pH, the basicity has no dramatic effect on the

Table 2. pK_a, Activity, Selectivity for 5−8

compd	X	n	pK_a[a]	α7 activity[b] pEC$_{50}$ ± SEM (n)	selectivity[b] pIC$_{50}$ (μM) α1	α3	5HT3
5	CH$_2$	1	9.4	6.38 ± 0.05 (5)	<4.5	<4.5	<4.5
6	CH$_2$	2	9.6	6.04 ± 0.04 (2)	<4.5	5.1	<4.5
7	O	1	7.2	5.18 ± 0.11 (2)	NT	NT	NT
8	O	2	8.6	5.93 ± 0.02 (2)	NT	NT	NT

[a]pK_a was calculated using ACD/pKa DB, release 12.00. [b]All functional activities were measured in a calcium flux assay. Only compounds with α7 pEC$_{50}$ higher than 6 were considered suitable for the selectivity evaluation. NT indicates not tested.

α7 activity.[11] This observation is in agreement with the results reported in Table 2 where the least active compound **7** is the one with the weakest basic center.

The steric hindrance, exemplified by the modulation of the ring size, has limited impact on the α7 activity; no relevant loss of potency is noted moving from **5** to **6** and from **7** to **8**. Compound **5**, bearing a piperidine moiety, was the most promising in terms of α7 activity and selectivity for the subsequent SAR investigation (no agonist activity was ever observed on the α1, α3, and 5HT3 receptors for any of the compounds tested).

The exploration of the second ring of the biaryl system was the next focus. A series of collected data are reported in Table 3. In general, these modifications modestly affected α7

Table 3. ClogP, Activity, and hERG inhibition for 5−12

Compd	R	ClogP	α7 Activity[a] pEC$_{50}$ ± SEM (n)	hERG[b] IC$_{50}$ (μM)
5	(4-methoxyphenyl)	3.3	6.38 ± 0.05 (5)	4.61
9	(tert-butyl)	2.9	<4.5	NT
10	(3-methoxyphenyl)	3.3	6.33 ± 0.07 (2)	3.08
11	(3-fluorophenyl)	3.5	6.08 ± 0.04 (2)	1.29
12	(fluoropyridyl)	2.3	6.13 ± 0.06 (2)	15.8

[a]All functional activities were measured in a calcium flux assay. [b]hERG response was obtained from CHO cells stably expressing the channel. NT indicates not tested.

activity, and when the phenyl ring was replaced by an alkyl group, such as in **9**, complete loss of activity was recorded. The related receptors (α1, α3, and 5HT3) were usually unaffected. Limited and unpredictable activity was sometimes observed for α3 and α1 such as in **10** and **11**, respectively (Table 1, Supporting Information). Compounds **5**, **10**, and **11** were advanced into our ADME characterization stage, and they proved to have a fair overall profile (Table 2, Supporting Information).

Interestingly the 3CC analogues showed a consistent improvement of the plasma stability compared with the corresponding 4CC counterpart (**1** and **3** Table 2, Supporting Information). We made the hypothesis that the closer proximity of the basic center to the amide bond in the 3CC analogues results in decreased affinity for the proteases/esterase binding site compared to the 4CC analogues. These result in lower amide hydrolysis rates.

The most promising of these molecules were also characterized in a hERG inhibition assay; **5**, **10**, and **11** presented some inhibition (Table 3), indicating a potential cardiac toxicity.

In light of the known effect of the ClogP on the hERG inhibition,[13] we decided to modulate this parameter in our compounds by means of single point modifications. As the replacement of a phenyl ring with the corresponding pyridyl gives an approximate ClogP reduction of 1 log unit, we

synthesized the pyridine analogue of **11**, compound **12** (Table 3), having an acceptable hERG inhibition (15.8 μM).

Compound **12** displayed physicochemical properties (MW, ClogP, ClogD, and MPSA) predictive of good brain penetration and a promising ADME profile (Table 3, Supporting Information). The molecule met all the desired criteria to be advanced to PK studies, where it showed moderate clearance (23 mL min^{-1} kg^{-1}), excellent bioavailability, and a rapid absorption. This is demonstrated by the T_{max} that occurs within 1 h of dosing. The BBB assessment highlights a good brain penetration with good brain levels (C_{max} of 55 ng/g).

The affinity of **12** for its target was confirmed in a binding assay using the rat receptor (0.39 μM), while the potency was further demonstrated in electrophysiological studies in rat and human receptor expressing cell lines (10.7 and 10.0 μM, respectively, full agonist functional responses). The difference (14-fold) between the EC$_{50}$ values, obtained using the oocyte expression system (10.7 μM) and the calcium influx methodology (0.74 μM), is in line with other literature observations. This could be ascribed to an overestimation of the EC$_{50}$ values recorded in electrophysiology.[14,15] In addition, **12** (evaluated at 10 μM) showed inhibition of < 50% in a panel of 70 receptors with the only exception of the α2a, α2b, α2c adrenergic receptors and the H3 histaminic receptor (% inhibition at 10 μM: 73, 64, 57, and 62, respectively). Good selectivity profile was then confirmed when these results are compared to the functional ion-flux EC$_{50}$.

In light of the optimal results obtained, **12** was evaluated in in vivo efficacy models. The molecule displayed efficacy in a rat model of cognitive functions, in particular a form of episodic memory measured in the novel object recognition test (NOR, Figure 2A). In perceptual processing **12** showed the ability to attenuate pharmacologically induced deficits via the glutamatergic system in a prepulse inhibition rat model

Figure 2. Induced memory enhancement of **12** in NOR using spontaneous decay of memory (24 h time interval) as amnesic factor in rats: blue columns, exploration time of new object; red columns, exploration time of familiar object; (A) effects of several doses of **12** administered orally 30 min before T1 exploration; (B) reversion of memory enhancement induced by **12** using pretreatment (5 min before the orally administration of **12** at 3 mg/kg) with MLA.

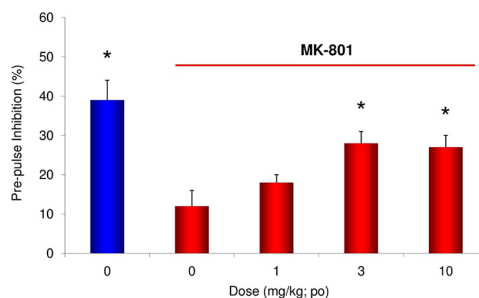(PPI, Figure 3), a classic paradigm for evaluating potential treatment for schizophrenia.

Figure 3. Ability of **12** to normalize an MK-801 induced disruption of PPI of the acoustic startle response in rats: blue column, vehicle, no MK-801; red columns, vehicle or **12** at several doses administered orally.

Treatment with **12** induced memory enhancement in the NOR at several doses when administered orally using a 24 h delay time as amnesic factor, with a minimum efficacious dose of 3 mg/kg po (Figure 2A). Importantly, the induced memory enhancement in the NOR experiment was blocked by pretreatment with the α7 antagonist methyllycaconitine (MLA, 5 mg/kg ip), demonstrating the direct involvement of the α7 nAChR (Figure 2B). Moreover, **12** reversed a dizocilpine (MK-801, 0.085 mg/kg po) induced deficit in PPI with a minimum efficacious dose of 3 mg/kg po. (Figure 3).

It is known that the brain concentrations of other α7 agonists (for example, PHA-543,613)[16] to achieve efficacy in vivo during behavioral tests are unable to activate α7 nAChRs in vitro. Recently the positive outcome of in vivo experiments, even at in vitro subpharmacological doses, has been interpreted as coagonist activity of EVP-6124 with acetylcholine on α7 nAChRs.[17] To benchmark our compound in this respect, we attempted some pharmacokinetic/pharmacodynamic considerations. After a single oral dose of 3 mg/kg, corresponding to the minimum efficacious dose in both our behavioral in vivo tests (NOR and PPI), **12** achieved a free brain concentration of 33 nM.[18] The fold EC$_{50}$ of 0.045, calculated as the ratio between the unbound concentration in the brain (C_{fu} brain, 33 nM) and the α7 EC$_{50}$ (740 nM), indicates that in vivo efficacy is achieved at brain levels that are a small fraction of the EC$_{50}$. This observation is in agreement with the previously mentioned literature stating that limited receptor activation is enough to obtain in vivo efficacy.[17]

In terms of safety, **12** was subjected to a preliminary toxicology assessment with a 7-day tolerability study in rat and found to be well tolerated up to a dose of 100 mg kg^{-1} day^{-1}.

In conclusion, the overall characterization of **12** demonstrated good in vitro properties, optimal in vivo efficacy, and a low toxicity risk. In particular, the minimum efficacious dose in conjunction with the tolerability study promises the potential for a wide therapeutic window.

■ CHEMISTRY

All the compounds investigated were prepared using two general synthetic strategies (route A and route B).

Route A (Scheme 1) consisted of a three-step synthesis: commercially available 4-bromobutyric acid ethyl ester (**13**)
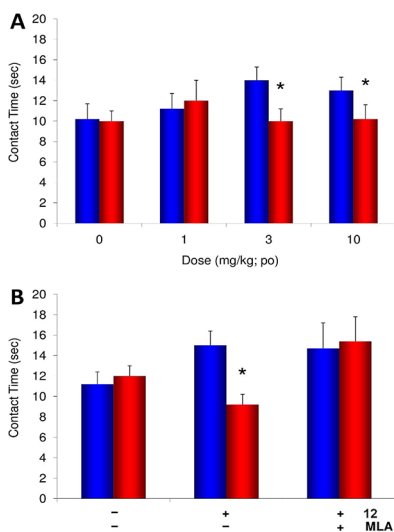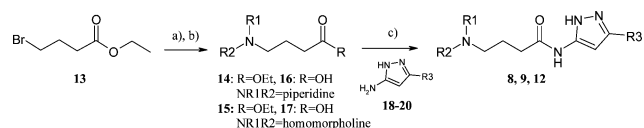
**Scheme 1. Synthesis of 4-Aminobutyric Acid Amide via Route A**[a]

[a] (a) R1R2NH, toluene, reflux; (b) NaOH, water, reflux; (c) CDI, 1,2-dichloroethane, 50 °C.

was reacted through a nucleophilic substitution with different amines to afford the corresponding amino esters (**14** and **15**), which were then hydrolyzed with NaOH to give the desired 4-aminobutyric acids (**16** and **17**). The amino acids obtained were activated with *N*,*N*′-carbonyldiimidazole and coupled to 3-aminopyrazoles (**18−20**, Chart 1, Supporting Information) in dichloroethane to afford the targeted products aminobutyric acid amide (**8**, **9**, and **12**).

Route B (Scheme 2) was a one-pot synthesis comprising amide coupling between *ω*-bromoalkanoyl chlorides (**21a**,

Scheme 2. Synthesis of 5-Aminopentanoic acid Amide via Route B[a]
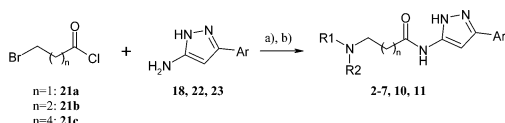
[a] (a) DIPEA, DMA, −10 °C; (b) R1R2NH, NaI, DMA, 50 °C.

21b, and **21c**) and 3-aminopyrazoles (**18**, **22**, and **23**, Chart 1, Supporting Information) in dimethylacetamide to give the corresponding 4-bromoalkanoylamides, followed by in situ addition of the desired amine and NaI to afford final compounds **2−7**, **10**, and **11**.

3-Aminopyrazoles **18**, **19**, and **22** were found to be commercially available. The synthesis of **20** and **23** is reported in the Supporting Information.

CONCLUSIONS

The evolution of a previously reported chemotype led us to the identification of **12** (SEN78702, WYE-308775). Although the activity of this compound was not improved compared to **1**, we fulfilled the original goals of the present work: improved plasma stability and brain penetration (compare data for **12** with data for previously reported **1**).[11]

Compound **12** is a novel *α*7 agonist, which exhibited overall an excellent balance of potency, selectivity, DMPK data, and brain penetration. Furthermore our lead molecule was demonstrated to improve cognitive function in a NOR test and to reverse a pharmacological disruption in a PPI test. In common with other reported *α*7 agonists, the in vivo pharmacological effects were observed at very low brain levels, sufficient to activate a small fraction of the receptors. The compound was furthermore complemented by a favorable safety profile as demonstrated by the 7-day toxicological study in rat.

In conclusion the collective preclinical package suggests potential interest for the progression and evaluation of **12** toward further studies and in a clinical setting for AD and schizophrenia and raises the interest in the exploration of novel analogues of **12** bearing a pyridyl ring.

EXPERIMENTAL SECTION

***N*-[5-(5-Fluoropyridin-3-yl)-2*H*-pyrazol-3-yl]-4-piperidin-1-ylbutyramide (12).** To a suspension of 4-piperidin-1-ylbutyric acid hydrochloride (175 mg, 0.84 mmol) in 1,2-dichloroethane (3 mL) was added *N*,*N*′-carbonyldiimidazole (136 mg, 0.84 mmol). The mixture was stirred at room temperature for 2 h (when activation of the amino acid was complete, dissolution of the suspension was generally observed). 5-(5-Fluoropyridin-3-yl)-2*H*-pyrazol-3-ylamine **20** (100 mg, 0.56 mmol) was added. The mixture was stirred for a further 10 h until reaction completion (as monitored by LC−MS). The solvent was washed with saturated Na_2CO_3 solution, extracted, and removed under reduced pressure. The crude product was purified by preparative HPLC to give 130 mg of the title compound as formate salt (61%, yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.39 (s, 1H), 8.30 (ddd, *J* = 9.7, 7.6, 1.9 Hz, 1H), 8.19 (dt, *J* = 5.0, 1.5 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.9 Hz, 1H), 6.87 (s, 1H), 3.21−3.09 (m, 4H), 2.60 (t, *J* = 6.7 Hz, 2H), 2.18−2.03 (m, 2H), 1.78 (d, *J* = 72.5 Hz, 8H). ^{13}C NMR/DEPT (101 MHz, methanol-d_4) δ 172.62, 159.78 (d, $^1J_{CF}$ = 245 Hz, C_{quat}), 148.12 (C_{quat}), 147.87 (d, $^2J_{CF}$ = 15 Hz, CH), 145.18 (C_{quat}), 139.88 (CH), 123.59 (CH), 115.84 (C_{quat}), 98.17 (CH), 58.30 (CH_2), 54.73 (CH_2), 34.05 (CH_2), 24.89 (CH_2), 23.31 (CH_2), 21.28 (CH_2). MS (ES) *m/z*: 332 (M + 1). UPLC (basic method): t_R = 0.71 min; area 100%. HRMS: calcd for $C_{17}H_{22}N_5OF$ + H$^+$, 332.188 11; found (ESI, [M + H]$^+$ obsd), 332.188 14.

ASSOCIATED CONTENT

ⓢ Supporting Information

General procedures, characterization data for all new compounds, additional properties for **1**, **3**, and **5−12**, and biological assay procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*Phone: +39 0577381474. Fax: +39 0577381323. E-mail: riccardozanaletti@hotmail.com.

Notes
The authors declare no competing financial interest.

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ABBREVIATIONS USED

AD, Alzheimer's disease; CC, carbon chain; CHO, Chinese hamster ovary; DMPK, drug metabolism and pharmacokinetics; ESI, electrospray ionization; hERG, human ether-a-go-go related gene; HRMS, high resolution mass spectrometry; MPSA, molecular polar surface area; nAChR, nicotinic acetylcholine receptor; NOR, novel object recognition; PPI, prepulse inhibition; t_R, retention time; SAR, structure−activity relationship

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(18) Calculated as $[C_{max}(\text{brain})][(100 - \text{PB rat})]/100$, where $C_{max}(\text{brain})$ is in nM.