Bioorganic & Medicinal Chemistry Letters 23 (2013) 1684–1688

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of a novel series of quinolone α7 nicotinic acetylcholine receptor agonists

Ivar M. McDonald *, Robert A. Mate, F. Christopher Zusi, Hong Huang, Debra J. Post-Munson, Meredith A. Ferrante, Lizbeth Gallagher, Robert L. Bertekap Jr., Ronald J. Knox, Barbara J. Robertson, David G. Harden, Daniel G. Morgan, Nicholas J. Lodge, Steven I. Dworetzky, Richard E. Olson, John E. Macor

Bristol–Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492-7660, USA

ARTICLE INFO

Article history:
Received 7 December 2012
Revised 11 January 2013
Accepted 16 January 2013
Available online 29 January 2013

Keywords:
α7 Nicotinic acetylcholine receptor
Schizophrenia
Efflux
Basicity

ABSTRACT

High throughput screening led to the identification of a novel series of quinolone α7 nicotinic acetylcholine receptor (nAChR) agonists. Optimization of an HTS hit (**1**) led to 4-phenyl-1-(quinuclidin-3-ylmethyl)quinolin-2(1*H*)-one, which was found to be potent and selective. Poor brain penetrance in this series was attributed to transporter-mediated efflux, which was in turn due to high pK_a. A novel 4-fluoroquinuclidine significantly lowered the pK_a of the quinuclidine moiety, reducing efflux as measured by a Caco-2 assay.

The α7 nicotinic acetylcholine receptor (nAChR) has been a target of significant and growing interest in neuroscience research for more than two decades as evidence has accumulated that it may be a viable target for treating the cognitive deficits and negative symptoms seen in schizophrenia.[1–3] Although current antipsychotic medications are able to manage the positive symptoms of schizophrenia (e.g., hallucinations, delusions), no treatments exist which alleviate the negative symptoms (e.g., reduced affect, anhedonia, social withdrawal) or cognitive deficits which are also core features of the disorder. Several α7 nAChR agonists have demonstrated improvement in preclinical models of memory and cognition, and a few examples have shown signs of alleviating both cognitive deficits and negative symptoms in clinical trials for schizophrenia.[2] α7 nAChR agonists have also become targets of interest for alleviating the cognitive deficits seen in Alzheimer's disease and as anti-inflammatory agents.[2,4]

Several known α7 nAChR agonists are shown in Figure 1.[5–7] Acetylcholine (ACh) is the natural ligand for the α7 nAChR, and most of the known α7 nAChR agonists can be considered ACh mimetics, containing a carbonyl or carbonyl isostere connected by a three-atom linker to a basic amine, expected to be highly charged at physiological pH.

A high-throughput screen of the Bristol–Myers Squibb compound collection for α7 nAChR agonists was performed using a Fluorometric Image Plate Reader (FLIPR) that measured calcium ion influx in HEK293 cells expressing the rat α7 nAChR.[8,9] Quinolone **1** (Fig. 2) was identified as a novel α7 nAChR agonist (α7 EC_{50} = 1.3 μM). Although the potency was only modest, we were

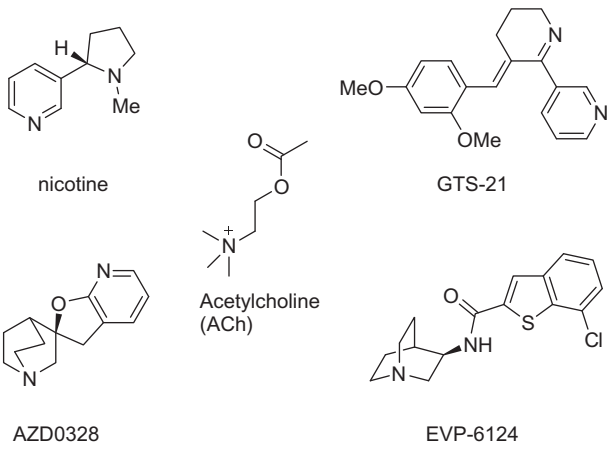


Figure 1. Examples of known α7 nAChR agonists.

* Corresponding author. Tel.: +1 203 677 5658; fax: +1 203 677 7884.
E-mail address: ivar.mcdonald@bms.com (I.M. McDonald).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.01.070

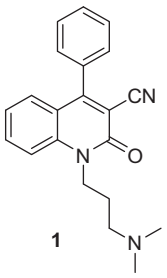
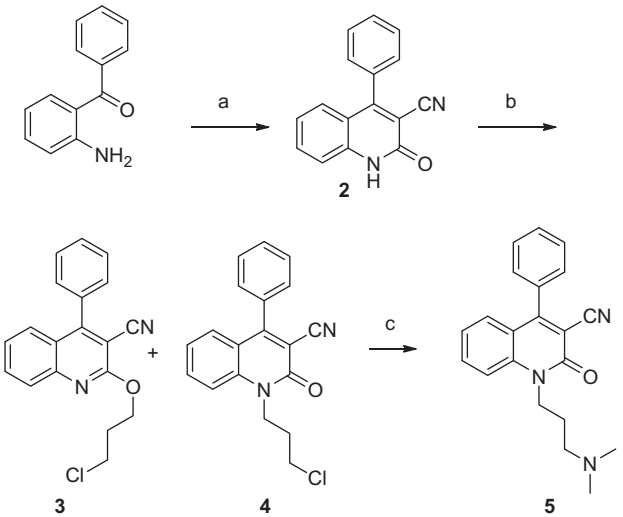
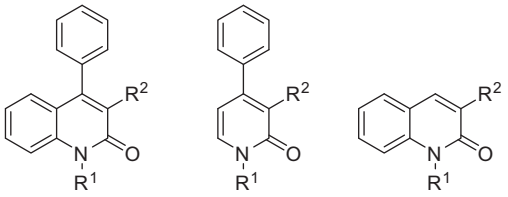


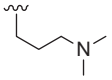
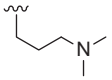
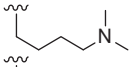
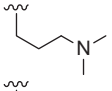
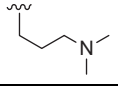
Figure 2. Lead compound from high-throughput screen.



Scheme 1. Reagents and conditions: (a) cyanoacetic acid, PCl_5,CH_2Cl_2, reflux 30 min, then NaOH (87%); (b) NaH, 3-chloro-1-iodopropane, DMF, rt, 3.5 h (3:21%, 4:38%); (c) dimethylamine, THF, NaI (cat) 70 °C, 4 h (60%).

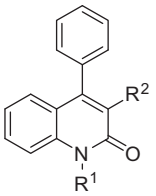
Table 1
α7 nAChR FLIPR data for selected compounds

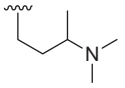
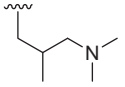
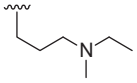
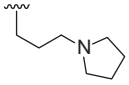
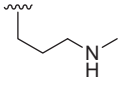
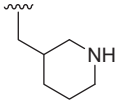
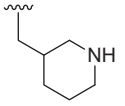
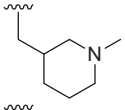
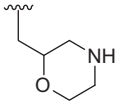
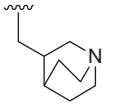


Compd	R^1	R^2	α7 nAChR EC_{50}[a] (μM)
1		CN	1.3
8		H	2.8
9		H	>10
10		H	>10
11		CN	>10
12		CN	>10

[a] All values are averages of at least two independent experiments.

Table 2
SAR of amine analogs



Compd	R^1	R^2	α7 nAChR EC_{50}[a] (μM)
13[b]		H	>10
14[b]		H	>10
15		CN	4.3
16		CN	9.3
17		CN	0.90
18[b]		CN	0.46
19		H	0.21
20[b]		CN	>10
21[c]		H	0.26
22[c]		H	0.15

[a] All values are averages of at least two independent experiments.
[b] Racemic.
[c] Homochiral, final compounds separated by chiral supercritical fluid chromatography (SFC). Data reported for more potent enantiomer (absolute configuration not determined).

encouraged by good selectivity (EC_{50}s >100 μM at α3β4, α4β2 and α1β1δε; IC_{50} = 19 μM at the closely related $5HT_3$ receptor), relatively low molecular weight (331 g/mol) and novelty compared to other known α7 agonists. Another interesting aspect of quinolone **1** was that the 4 atom linker connecting the basic amine and carbonyl moieties was longer than those present in most known agonists (see Fig. 1 for comparison).[10]

The initial route to quinolone **1** and analogs varying at the amine or in linker length followed along the lines of the previously reported synthesis (Scheme 1).[11] Thus, acylation of *o*-aminobenzophenone with cyanoacetic acid followed by intramolecular Knoevenagel condensation led to cyanoquinolone **2**, which was treated with sodium hydride and iodochloropropane to afford a separable mixture of the O- and N-alkylated compounds (**3, 4**).