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(*S*)-(−)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine Maleate (SIB-1508Y): A Novel Anti-Parkinsonian Agent with Selectivity for Neuronal Nicotinic Acetylcholine Receptors

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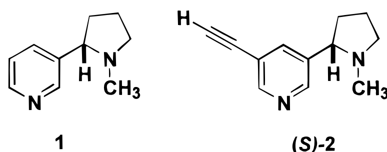
The selective modulation of neuronal receptor subtypes has considerable potential for the treatment of disease with minimal adverse side effects. Specifically, the ideal central nervous system (CNS) drug would discriminate not only between the target receptor and those in the periphery but also between receptor subtypes within the brain.[1] The importance of nicotinic acetylcholine receptors (NAChRs)[2,3] in several disease states, including Alzheimer's disease (AD)[4,5] and Parkinson's disease (PD),[6,7] is now well established. Indeed the NAChR agonist ABT-418 is presently in clinical trials for the treatment of AD.[8] In this communication, the synthesis and pharmacological evaluation of (*S*)-(−)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine [(*S*)-**2**, SIB-1508Y], a novel agonist of human neuronal NAChRs, are reported.[9] The characterization of this compound was accomplished using both classical methods and functional assays employing mammalian cell lines expressing NAChRs comprised of recombinant human NAChR subunits.



Initial structure−activity studies focused on the prototypical NAChR agonist nicotine (**1**).[10] Synthetic targets designed to probe the topology of the binding site of **1** revealed that substitution at the 5-position led to derivatives, such as racemic 5-bromo-3-(1-methyl-2-pyrrolidinyl)pyridine (**5**),[11] that had attractive pharmacological profiles. Compound **5** was therefore selected for further elaboration, and taking advantage of the aryl bromide functional group, a series of 5-substituted analogues was prepared. From this series 5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine fumarate (**2**, SIB-1765F) and 5-ethyl-3-(1-methyl-2-pyrrolidinyl)pyridine (**7**) were selected for biological evaluation and comparison with **1** and **5**.

Racemic **2** and **7** were synthesized according to Scheme 1. The reported synthesis of **5**[11,12] was modified to provide an efficient route to this key intermediate. Thus, treatment of readily available **3** with 1-vinylpyrrolidinone anion followed by decarboxylation and ring closure of the intermediate gave the imine **4**. Reduction ($NaBH_4$) and *N*-methylation under Eschweiler−Clarke conditions[13] afforded **5**.[14a] Palladium-catalyzed cross-coupling[15] of **5** with 2-methyl-3-butyn-2-ol provided the 5-alkynyl derivative **6** which underwent base-catalyzed deprotection[16] to give **2**.[14b] Conversion of **2** to **7** was achieved by hydrogenation (H_2, Pd−C).[14b] In order to evaluate the relative contributions of the individual enantiomers [(*S*)-**2** and (*R*)-**2**] to the activity of the racemate (**2**), the synthesis was modified to provide the component isomers separately (Scheme 1). Reduction of **4** with $NaBH_4$/CBZ-D-proline[17,18] followed by *N*-methylation provided enantiomerically enriched **5** (30% ee) which was crystallized as the dibenzoyl-L-tartrate salt to give, after Pd-mediated alkyne coupling and deprotection, (*S*)-**2** in >99% ee.[14c] Similarly, the use of $NaBH_4$/CBZ-L-proline, followed by crystallization with di-*p*-toluoyl-D-tartaric acid, ultimately provided the antipode (*R*)-**2** (97% ee).[14d,19]

The results of the binding and *in vitro* dopamine (DA) release experiments with **1**, **2**, **5**, and **7** are presented in Table 1. The data indicate that all the compounds tested exhibited a high degree of selectivity for the [^{3}H]-Nic (nicotine) binding site compared with the [^{3}H]QNB (muscarinic) binding site in rat cortical membranes. Differences were observed, however, in the ability of the compounds to release DA from rat striatal slices. Whereas **2** tended toward a greater efficacy than **1** in this bioassay, **7** was significantly less active. Furthermore, the data demonstrate that (*S*)-**2** was the enantiomer exhibiting the highest affinity in the binding assay and was primarily responsible for the DA release stimulated by **2**, an effect which is blocked by the NAChR antagonists mecamylamine and dihydro-β-erythroidine.[23] The results illustrate the utility of a functional assay for the differentiation of two closely related analogues (**2** and **7**) and led to the decision to more fully evaluate **2** and (*S*)-**2**.

Electrophysiological recording of current responses in *Xenopus* oocytes expressing recombinant human NAChRs is a sensitive assay for detecting the activity of agonists or antagonists. Thus voltage clamp recordings of oocytes expressing human $\alpha2\beta2$, $\alpha2\beta4$, $\alpha3\beta2$, $\alpha3\beta4$, $\alpha4\beta2$, $\alpha4\beta4$, or $\alpha7$ NAChR subtypes were obtained (Figure 1).[24] The inward current elicited by **2** was normalized to the response produced by a prior application of acetylcholine (ACh; 10 μM) to the same cell. At a concentration of 10 μM, **2** produced currents that ranged between 20% and 50% of the response elicited by ACh (10 μM) in oocytes expressing the $\alpha2\beta2$, $\alpha2\beta4$, $\alpha3\beta2$, $\alpha4\beta2$, and $\alpha4\beta4$ NAChR subtypes. No detectable inward currents were observed at the human $\alpha7$ receptor subtype,[25] and only a minimal response at the $\alpha3\beta4$ subtype was detected. This contrasts with **1** (data not shown) which is a potent agonist at both the $\alpha3\beta4$ and $\alpha7$ receptor subtypes in this assay.[27]

A functional assay employing cell lines stably expressing human recombinant NAChR[28,29] subtypes provided further data comparing **1**, **2** (*S*)-**2**, and (*R*)-**2**. In this assay, the activation of recombinant receptors by agonists stimulates calcium entry into cells. The subsequent elevation of cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) is determined by measuring the changes in fluorescence

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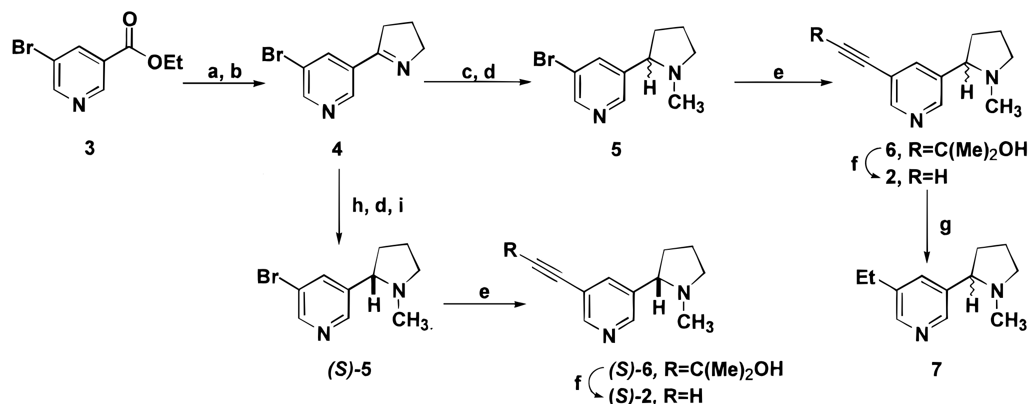
Scheme 1[a]



[a] (a) LiN(TMS)$_2$, 1-vinylpyrrolidinone, THF, 25 °C (99% yield); (b) 6 M HCl, Δ (71% yield); (c) NaBH$_4$, MeOH, HOAc (90% yield); (d) 37% HCHO (aq), HCO$_2$H, Δ (92% yield); (e) 2-methyl-3-butyn-2-ol, 10% Pd−C, CuI, PPh$_3$, K$_2$CO$_3$, DME, H$_2$O, Δ (92% yield); (f) NaH (cat.), PhMe, Δ (97% yield); (g) H$_2$, 10% Pd−C, MeOH (92% yield); (h) CBZ-D-proline, NaBH$_4$, CH$_2$Cl$_2$ (98% yield, 30% ee); (i) dibenzoyl-L-tartaric acid, EtOH−EtOAc (93% yield, >99% ee).

Table 1. Binding and Release Data[a]

compd	IC$_{50}$ (nM; mean ± SEM) [^{3}H]Nic[b]	[^{3}H]QNB[c]	release (±SEM) [^{3}H]DA[d]
1	4 ± 1.2	360 000 ± 40 400	100
5	19 ± 4	16 000 ± 2300	69 ± 11
2	4.6 ± 0.9	10 100 ± 1200	143 ± 11
7	11 ± 1.7	5800 ± 870	27.5 (26, 29)[e]
(*S*)-**2**	3 ± 0.5	8900 ± 980	163 ± 28
(*R*)-**2**	75 ± 1.7	4500 ± 120	55 ± 15

[a] The data represent the mean values from three independent experiments ($n = 3$). [b] Binding affinities at NAChRs were determined by measuring the displacement of [^{3}H]nicotine ([^{3}H]Nic) from a preparation of rat cortical membranes according to the procedure of Flynn and Mash.[20] [c] Muscarinic receptor binding (rat cortical membranes) was determined by displacement of [^{3}H]quinuclidinyl benzylate ([^{3}H]QNB) using the method of Yamamura and Synder.[21] [d] The efficacy of the compounds (300 μM) to stimulate [^{3}H]dopamine ([^{3}H]DA) release was determined using a preparation of superfused rat striatal slices as described by Sacaan *et al.*[22] The data are expressed as a percentage of the [^{3}H]DA release elicited by a maximally efficacious dose of nicotine (10 μM). [e] Mean value from two independent experiments, raw data in parentheses.

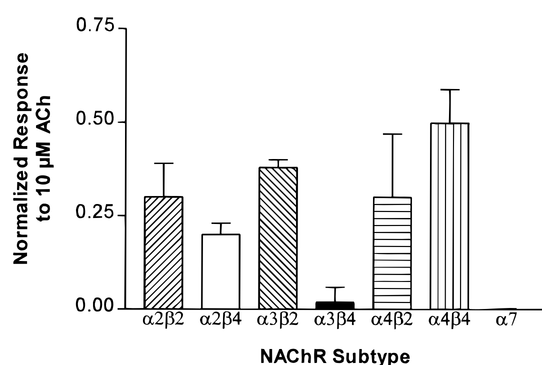


Figure 1. Voltage clamp recordings in *Xenopus* oocytes, the current evoked by **2** (10 μM) in *Xenopus* oocytes expressing the designated recombinant human NAChR subtypes. The ordinate shows the fractional response relative to 10 μM ACh.

of the Ca^{2+}-sensitive dye 1-[2-amino-5-(2,7-dichloro-6-hydroxy-3-oxy-9-xanthenyl)phenoxy]-2-(2-amino-5-methylphenoxy)ethane-*N,N,N,N*-tetraacetic acid (fluo-3).[30] The compounds were tested in cell lines expressing recombinant human α2β4, α3β4, α4β4, and α4β2 NAChR subtypes and a cell line expressing the fetal form (α1β1γδ) of human neuromuscular NAChRs (Tables 2 and 3).[31] In each cell line **1**, **2**, and (*S*)-**2** elicited increases in [Ca^{2+}]$_i$, and these effects were blocked by

Table 2. Profile of NAChR Agonist Functional Potency

compd	EC$_{50}$ (μM; mean ± SEM) (*n*) α2β4[a]	α3β4[a]	α4β4[a]	α4β2[a]	α1β1γδ[b]
1	10 ± 2 (3)	51 ± 2 (3)	7.1 ± 1.8 (3)[c]	2.1 ± 0.6 (5)[c]	65 ± 18 (3)
2	15 ± 3.6 (7)	41 ± 7 (8)	25 ± 7 (6)[c]	2.6 ± 1 (7)[c]	52 ± 6 (3)
(*S*)-**2**	5 ± 1.4 (3)	23 ± 2 (3)	9 ± 4 (3)	1.8 ± 0.7 (4)	nd
(*R*)-**2**	29 ± 8 (3)	68 ± 7 (3)	31 ± 6 (3)	inactive[d]	nd

[a] Human embryonic kidney (HEK293) cells. [b] Human RD cells. [c] See ref 23. [d] Highest concentration = 300 μM. Data derived from measured changes in [Ca^{2+}]$_i$ in cell lines stably expressing the designated human recombinant NAChR subtypes in response to compounds **1**, **2**, (*S*)-**2**, and (*R*)-**2**. n = number of determinations.

Table 3. Profile of NAChR Agonist Efficacy

compd	efficacy (mean ± SEM) (*n*) α2β4[a]	α3β4[a]	α4β4[a]	α4β2[a]	α1β1γδ[b]
2	39 ± 3 (7)	34 ± 4.2 (8)	23 ± 4 (6)	47 ± 10 (7)	53 ± 17 (3)
(*S*)-**2**	49 ± 5.2 (3)	52 ± 7.5 (3)	26 ± 10.4 (3)	49 ± 8.5 (4)	nd
(*R*)-**2**	9 ± 1.7 (3)	7 ± 2.3 (3)	8 ± 4 (3)	inactive[c]	nd

[a] Human embryonic kidney (HEK293) cells. [b] Human RD cells. [c] Highest concentration = 300 μM. Data derived from measured changes in [Ca^{2+}]$_i$ in cell lines stably expressing the designated human recombinant NAChR subtypes in response to compounds **2**, (*S*)-**2**, and (*R*)-**2**. The data are expressed as a percentage of the value for the maximally effective concentration of nicotine (**1**) in each cell line. n = number of determinations.

the NAChR antagonists *d*-tubocurarine and mecamylamine (data not shown). While (*S*)-**2** showed its greatest potency at the α4β2 NAChR subtype (Table 2), (*R*)-**2** exhibited low activity in the β4-containing cell lines and was inactive in the cell line expressing the α4β2 subtype. Furthermore, at a maximally efficacious concentration, (*S*)-**2** was 26−52% as efficacious as **1** in each cell line, whereas (*R*)-**2** displayed weak efficacy (Table 3). The data establish that (*S*)-**2** is the more active enantiomer which is in agreement with the binding and DA release results (Table 1).

Since **2** stimulated the release of DA from rat striatal slices, it was evaluated in an animal model of Parkinson's disease. The effect of **2** on ipsilateral rotations of rats with unilateral nigrostriatal 6-hydroxydopamine (6-OHDA) lesions[32] (rat-turning model) is shown in Table 4. At a dose of 25 mg/kg given subcutaneously (sc), **2** produced a significant increase in ipsilateral rotations compared with saline-treated animals, an effect which is blocked by mecamylamine. Futhermore, **2** was more efficacious than **1** at the maximum effective dose with

Table 4. Data for the Rat-Turning Model

compd	$dose_{max}$[a]	rotations (±SEM)	% rotations[b]
1	0.4	62 ± 21	100
2	25	163 ± 44[c]	263

[a] Maximally effective dose (mg/kg free amine, sc). Intolerable side effects were observed for nicotine (**1**) at a dose of 1 mg/kg. [b] Ipsilateral rotations measured over a period of 120 min, expressed as a percentage of the value for **1**. [c] $p \le 0.05$ (Student's *t*-test). Each group contained eight animals.

minimal adverse side effects. These studies led to the preclinical development of (*S*)-**2** for the treatment of PD.

In conclusion, the novel NAChR agonist (*S*)-**2** has been synthesized and evaluated in a range of *in vitro* and *in vivo* assays. Significantly, the differentiation of (*S*)-**2** from structurally related agonists with quite similar binding affinities for endogenous NAChRs was accomplished on the basis of results derived from functional assays, including a novel functional assay employing cell lines stably expressing recombinant human NAChR subtypes. This assay provides a powerful method for the discovery of subtype selective NAChR agonists and antagonists, acting either at the ACh binding site or at novel allosteric sites on the receptor complex.[33]

Supporting Information Available: Experimental Section (17 pages). Ordering information can be found on any current masthead page.

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