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Bioorganic & Medicinal Chemistry Letters 18 (2008) 188–193
Bioorganic & Medicinal Chemistry Letters

7-Azaindole derivatives as potential partial nicotinic agonists

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Received 5 September 2007; revised 25 October 2007; accepted 27 October 2007
Available online 1 November 2007

Abstract—We have investigated a series of 7-azaindoles as potential partial agonists of the α4β2 nicotinic acetylcholine receptor (nAChR). Three series of 7-azaindole derivatives have been synthesized and evaluated for rat brain neuronal nicotinic receptor affinity and functional activity. Compound **(+)-51** exhibited the most potent nAChR binding (K_i = 10 nM). Compound **30A** demonstrated both moderate binding affinity and partial agonist potency, thus representing a promising lead for the indications of cognition and smoking cessation.

Nicotinic acetylcholine receptors (nAChRs) are a subtype of acetylcholine-operated receptors and are members of the superfamily of ligand-gated ion channel receptors.[1] Pentameric combinations of multiple α and β subunits lead to a large number of nicotinic receptors in the brain, complicating their study.[2] The nAChR are involved in a wide range of physiological and pathophysiological processes. The numerous neuronal nAChRs subtypes are located at neurons throughout the CNS, where they are involved in a number of processes connected to cognitive functions, learning and memory, reward, motor control, and analgesia.[2] Equally important to the overall contribution of nAChRs to cholinergic neurotransmission are the roles of presynaptic and preterminal nAChRs as autoreceptors and heteroreceptors regulating the synaptic release of acetylcholine and other neurotransmitters including dopamine, norepinephrine, serotonin, glutamate, and γ-aminobutyric acid. Because of their modulatory influence on these neurotransmitter systems, neuronal nAChRs have been proposed as potential therapeutic targets for the treatment of pain, epilepsy, and a wide range of neuron-degenerative and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, schizophrenia, anxiety, depression and the treatment of smoking cessation.[3–5]

The invention of TC-2403,[6] as a moderately potent nicotinic receptor agonist exhibiting some functional preference for α4β2 over other α/β, α7, and muscle-type nAChRs, and the finding of TC-1734,[7] as a partial agonist on nicotinic receptor subtype α4β2 showing improved short- and long-term memory in rodent models,[8] encouraged us to synthesize 7-azaindole[9,10] derivatives (I–III, Fig. 1). It was envisaged that these conformationally restricted analogs of *trans*-meta-nicotine (TC-2403) would result in compounds with the traditional pharmacophoric elements for nAChR agonists, consisting of a charged nitrogen and a hydrogen bond acceptor,[11] with distinctive distance/angle geometries.[12]

An elegant example, which illustrates such a rigidification strategy, is varenicline, acting as a selective partial agonist of the α4β2 nAChR, displaying 30–60% of the in vivo efficacy of nicotine, and effectively blocking the

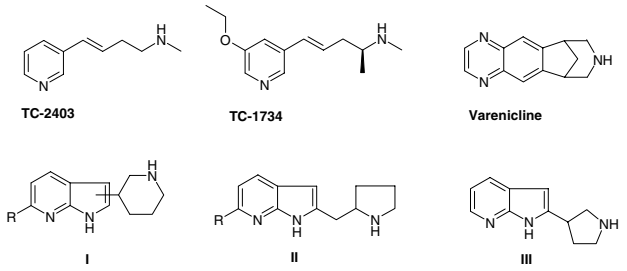

Figure 1.

Keywords: Azaindole derivatives; Partial agonist; Nicotinic acetylcholine receptor; Cognition; Smoke cessation.
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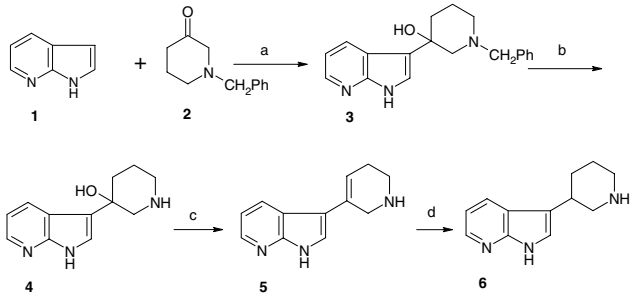
doi:10.1016/j.bmcl.2007.10.101

in vivo response to nicotine.[4b] This compound was approved by the FDA for smoking cessation in 2006.

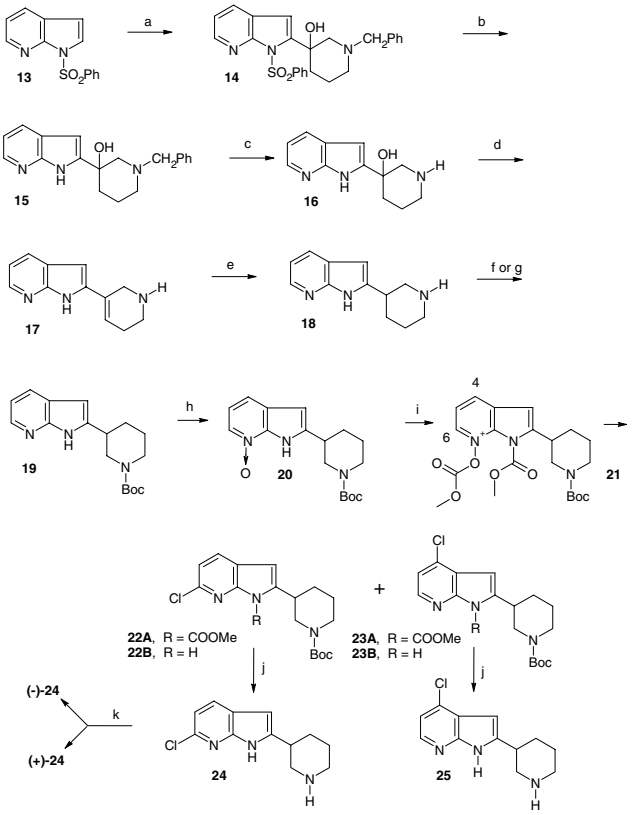
The investigation of the novel 7-azaindole derivatives (I–III) as putative partial nicotinic agonists is presented in this paper, and their synthetic routes are described in Schemes 1–7.

Commercially available 7-azaindole **1** (Scheme 1) was reacted with 1-benzyl-piperidin-3-one **2** under basic conditions to yield the piperidin-3-ol compound **3**.[9] Benzyl group deprotection with ammonium formate and palladium hydroxide resulted in **4**, which was dehydrated to **5** under acidic conditions. Hydrogenation gave the desired 3-piperidin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridine **6**.

The synthesis of 6-chloro-3-piperidin-3-yl-1*H*-pyrrolo-[2,3-*b*]pyridine **12** is depicted in Scheme 2. Compound **6** was reacted with di-*tert*-butyl-dicarbonate to generate the piperidine *N*-Boc protected analog **8** (in a two-step sequence), thereby facilitating the synthesis of the *N*-oxide **9**. Regioselective chlorination occurred at the C-6 position of 7-azaindole *N*-oxide **9** and was achieved by a Reissert–Henze type reaction, effectively assisted

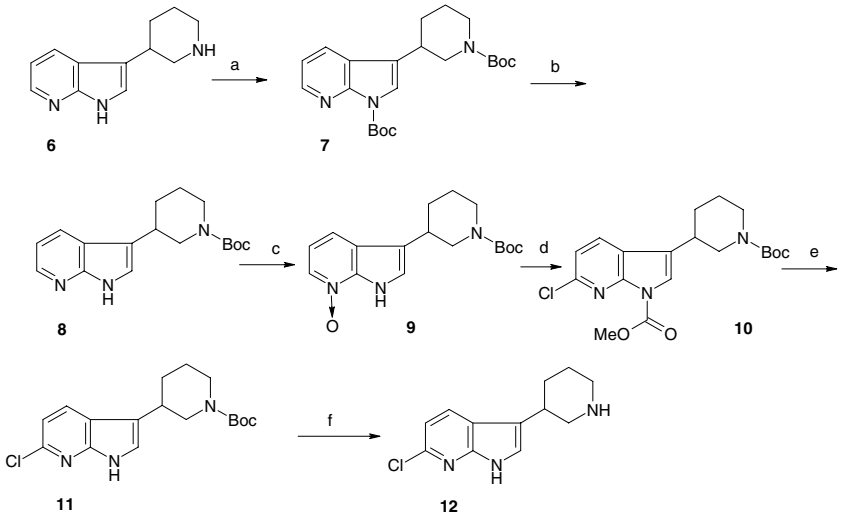


Scheme 1. Reagents and conditions: (a) NaOEt/EtOH, rt, 72 h (75%); (b) NH_4HCO_2, $Pd(OH)_2$, MeOH, reflux, 2 h (88%); (c) HCl/EtOH, reflux, 1 h (44%); (d) H_2, 50 psi, $Pd(OH)_2$, HCl/MeOH, rt, 1 h (55%).

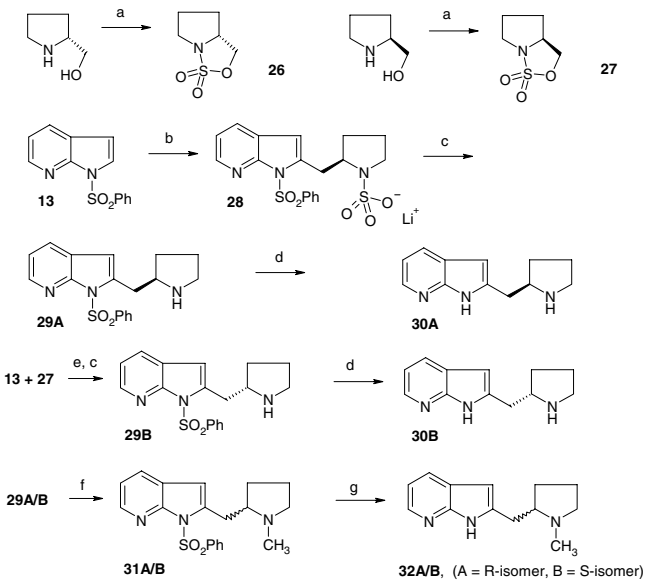


Scheme 3. Reagents and conditions: (a) 1—LDA/THF, −10 °C, 0.5 h; 2—1-benzyl-piperidin-3-one, THF, −30 °C, 2 h (23%); (b) 2 N NaOH in MeOH, reflux, 2 h (66%); (c) NH_4HCO_2, $Pd(OH)_2$, MeOH, reflux, 1 h (80%); (d) 6 N HCl, reflux, 18 h (92%); (e) H_2, 50 psi, $Pd(OH)_2$, MeOH, rt, 1 h (84%); (f) chiral column[23]; (g) 1—$(BOC)_2O$, $N(Et)_3$, CH_2Cl_2, reflux, 0.25 h; 2—2 N NaOH/MeOH, rt, 0.5 h (87%); (h) *m*-ClPBA, dimethoxyethane, rt, 0.25 h (87%); (i) HMDS, methyl chloroformate, THF, reflux, 1.5 h (34% (**22 A**) and 44% (**23A**)); (j) 1—2 N NaOH in MeOH, rt, 18 h; 2—HCl/EtOH, reflux, 1 h (31%); (k) chiral column.[24]

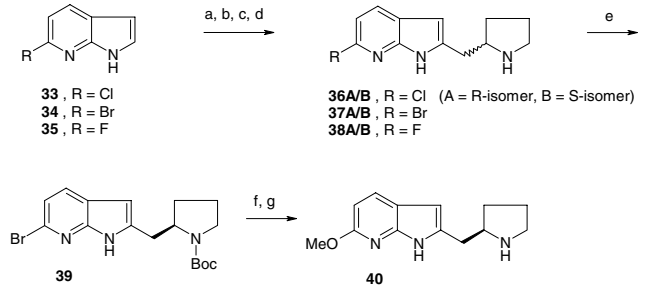
by hexamethyldisilazane (HMDS).[13] Thus, the *N*-1-methoxycarbonyl compound **10**, obtained from this



Scheme 2. Reagents and conditions: (a) $(Boc)_2O$, $N(Et)_3$, CH_2Cl_2, reflux, 0.25 h; (b) 2 N NaOH/MeOH, rt, 0.5 h (55% overall); (c) *m*-CPBA, dimethoxyethane, rt, 0.25 h (95%); (d) HMDS, methyl chloroformate, THF, rt, 0.5 h (59%); (e) 2 N NaOH/MeOH, rt, 18 h (95%); (f) HCl/EtOH, reflux, 1 h (76%).



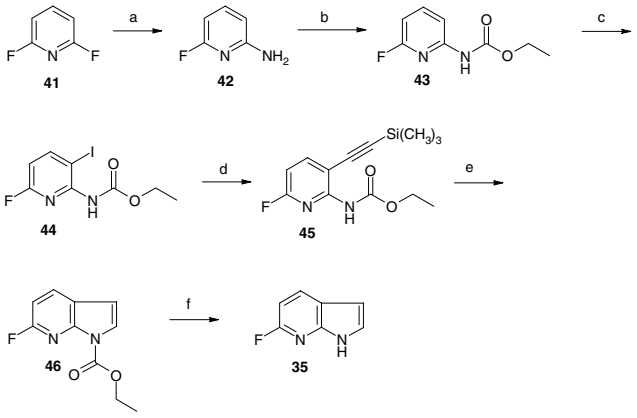
Scheme 4. Reagents and conditions: (a) SO_2Cl_2, Pyridine, CH_2Cl_2, −78 °C, 1 h[15] (35%); (b) 1—LDA/THF, −10 °C, 0.5 h; 2—(*R*)-sulfamidate, THF, −78 °C and then −20 °C, 2 h; (c) 1 N HCl, EtOH, THF, 80 °C, 18 h (44% overall); (d) KOH, hydrazine monohydrate, 2-(2-hydroxy-ethoxy)-ethanol, 100 °C, 1 h (66%)[25]; (e) 1—LDA/THF, −10 °C, 0.5 h; 2—(*S*)-sulfamidate, THF, −20 °C, 2 h; (f) 37% aqueous formaldehyde, $NaBH(OAc)_3$, dichloroethane, rt, 1 h (90%); (g) KOH, hydrazine monohydrate, 2-(2-hydroxy-ethoxy)-ethanol, 100 °C, 1 h (80%).[26]



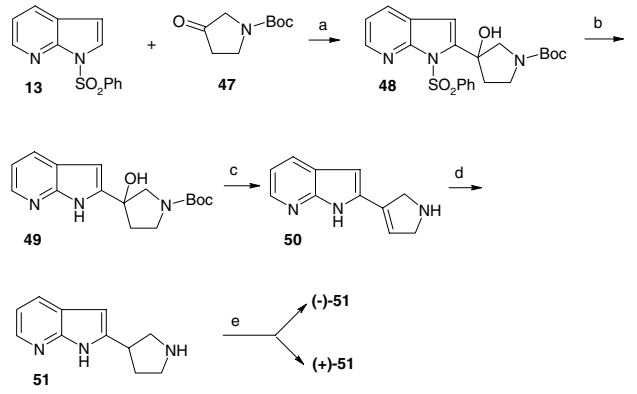
Scheme 5. Reagents and conditions: (a) 1—NaH/THF, 0 °C, 1 h; 2—benzenesulfonyl chloride, 0 °C, 1 h (resp. 80%, 95% and 89%); (b) 1—LDA/THF, −78 °C, 1 h; 2—(*R* or *S*)-sulfamidate, THF, −78 to 30 °C, 2 h; (c) 1 N HCl, EtOH, THF, 80 °C, 18 h (resp., 31%, 48% and 30%); (d) 2 N NaOH, isopropanol, 100 °C, 3 h (resp., 58%, 76% and 57%); (e) 1—$(BOC)_2O$, $N(Et)_3$, CH_2Cl_2, reflux, 0.25 h; 2—2 N NaOH/MeOH, rt, 0.5 h (79% overall); (f) NaOMe, Cu(I)Br, DMF, MeOH (56%); (g) HCl/EtOH, reflux, 1 h (80%).[27]

reaction, was converted to compound **11** under basic conditions. Acidic deprotection of the *N*-Boc completed the synthesis of **12**.

Scheme 3 highlights the synthesis of 2-(3-piperidyl) substituted azaindoles. The phenylsulfonyl group as Directing Metalation Group (DMG) at the *N*-1-position of azaindole analogs enabled the lithiation of the 2-position and thereby the synthesis of C-2 derivatives.[14] The C-2 lithio derivative of **13**, prepared on multigram scale by α-metalation (1,1 equiv LDA, THF, −10 °C), was trapped with 1-benzyl-piperidin-3-one (**2**) to afford **14**



Scheme 6. Reagents and conditions: (a) NH_4OH, 9.2 bar, 125 °C (90%)[18]; (b) ethyl chloroformate, K_2CO_3, CH_3CN, 40 °C, 96 h (66%); (c) 1—*n*-BuLi/THF, TMEDA, −78 °C, 2 h, 2—I_2, −78 °C, 1 h (70%); (d) TMSA, CuI, $PdCl_2(PPH_3)_2$, $N(Et)_3$, 100 °C, 10 h (42%); (e) CuI, DMF, 150 °C, 0.5 h (58%); (f) 2 N NaOH/MeOH (99%).



Scheme 7. Reagents and conditions: (a) 1—LDA/THF, −10 °C, 0.5 h; 2—$CeCl_3$, THF, −70 to 10 °C, 0.25 h; (3) compound **47**, THF, −30 °C, 2 h (58%); (b) KOH, hydrazine monohydrate, 2-(2-hydroxy-ethoxy)-ethanol, 100 °C, 1 h (84%); (c) 38% HCl/H_2O (1:1), reflux, 12 h (58%); (d) H_2, 50 psi, $Pd(OH)_2$, MeOH, rt, 2 h (59%); (e) chiral column.[28a]

(Scheme 3). After basic hydrolysis of the *N*-1-phenylsulfonyl group (**15**), the preferred sequence to **17** was benzyl group deprotection (**16**), subsequently followed by dehydration under acidic conditions. Hydrogenation yielded 2-piperidin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridine **18**.

Furthermore, by the sequence described in Scheme 3, starting material **18** was converted into the *N*-oxide **20** which was exposed to methyl chloroformate and HMDS.[13] Surprisingly, the subsequent Reissert–Henze reaction afforded a mixture of 6- and 4-substituted products (**22A** and **23A**). We attributed the non-selectivity of this reaction to steric and electronic influences of the piperidine ring on the adjacent carbamate and carbonate group in intermediate **21**, decreasing the reactivity of the 6-position relative to the 4-position. Purification by chromatography and subsequent basic hydrolysis (**22B**, **23B**), followed by removal of the *N*-Boc protecting group, yielded the corresponding 6- and 4-chloro-2-piperidin-3-yl-1*H*-pyrrolo[2,3-*b*]pyridines (**24**, **25**).

5-(*R*)-[3,3,0]-1-Aza-2-thia-3-oxabicyclooctane-2,2-di-oxide (**26**, Scheme 4) and the corresponding 5-(*S*)-analog (**27**)[15] were employed as enantiomerically pure starting materials for the synthesis of **30A** and **30B** (Scheme 4).

The 2-lithio derivative of **13** was reacted with (*R*)-sulfamidate **26** to produce the lithium-sulfonate **28**, which was subsequently hydrolyzed to generate **29A**. Various methods were tried for the removal of the *N*-1-phenylsulfonyl group. After considerable experimentation, we found that potassium hydroxide in di-ethylene glycol, in the presence of hydrazine, improved the reaction rate and yields of **30A**.[25a] The (*S*)-isomer **30B** was obtained starting from **13** and the (*S*)-sulfamidate **27**. Reductive methylation of **29A** (**29B**) resulted in **31A** (**31B**). Basic deprotection of the *N*-1-phenylsulfonyl group completed the synthesis of **32A** (**32B**).

Scheme 5 illustrates the preparation of the halogen and methoxy derivatives of **30A/B**. The procedure described above (Scheme 4, using the chiral sulfamidates **26** and **27**) was used to convert the *N*-1-phenylsulfonyl[14] protected derivatives of **33**,[13] **34**,[13] and **35** (Scheme 6) to the corresponding compounds **36A/B**, **37A/B**, and **38A/B**[16] (Scheme 5). The 6-bromo derivate **37A** was converted to its *N*-Boc protected analog **39** (as described in Scheme 1) which was treated with NaOMe in the presence of copper(I) bromide.[17] Subsequent deprotection of the *N*-Boc yielded (*R*)-6-methoxy-2-pyrrolidin-2-ylmethyl-1-*H*-pyrrolo[2,3-*b*]pyridine (**40**).

Surprisingly, and to the best of our knowledge, the synthesis of 6-fluoro-7-azaindole (**35**) has not been published yet. We envisioned a straightforward synthesis of **35** from commercially available 2,6-difluoro-pyridine **41**, which was converted to 2-amino-6-fluoro-pyridine **42**.[18] Different DMG groups were examined (for example the 2,2-dimethyl-propanamide),[17,19] the ethyl-carbamate[20] being essential for the regioselective iodination of compound **43** to generate the unknown (6-fluoro-3-iodo-pyridin-2-yl)-carbamic acid ethyl ester (**44**). Subsequent Sonogashira chemistry (**45**) and ring closure in the presence of copper(I) iodide[21] afforded compound **46**. Cleavage of the *N*-1-carbamate generated the desired 6-fluoro-7-azaindole **35**.

The preparation of 2-pyrrolidin-3-yl-1*H*-pyrrolo[2,3-*b*]-pyridine (**51**) is depicted in Scheme 7. The C-2 lithio derivative of **13** underwent a cerium-mediated reaction[22] with 3-oxo-pyrrolidin-1-carboxylic acid *tert*-butyl ester (**47**) to yield the corresponding tertiary alcohol (**48**). Basic hydrolysis of the phenylsulfonyl group resulted in compound **49**. Acidic deprotection of the *N*-Boc and subsequent dehydration generated **50**. Hydrogenation completed the synthesis of **51**. Chromatographic separation of the isomers could be achieved using a chiral column.[28a]

The binding affinities of the 7-azaindole analogs at the rat neuronal nicotinic receptors in the brain were determined using [3H]cytisine displacement experiments (Table 1).[29] We can readily observe that the 2- and 3-azaindole substituted piperidine derivatives (**18** and **6**) displayed low binding affinity. Electron-withdrawing substitution in heterocyclic nicotine derivatives has previously been reported to increase binding affinity[3] and/or improve subtype selectivity in terms of functional activity.[32] Interestingly, the 6-chloro analogs **12** and **(+)-24** exhibited the same affinity compared to their hydrogen analogs (**6** and **(−)-18**). Moreover, replacement of the piperidine ring (**(−)-18**) to a (methylene)-pyrrolidine ring, i.e., **30A** and **(+)-51**[28a,b] resulted in a 16-fold and 200-fold affinity increase, respectively.

Table 1. Radioligand [3H]cytisine binding for 7-azaindole analogs[29]

Compound	K_i[a] (nM)	Compound	K_i[a] (nM)
6	2950	**36A**	147
12	2950	**36B**	3715
(±)-18	10,000	**37A**	691
(+)-18	na	**37B**	na
(−)-18	1995	**38A**	316
(±)-24	na	**38B**	1995
(−)-24	na	**40**	na
(+)-24	3460	**(±)-51**	16
25	na	**(−)-51**	251
30A	125	**(+)-51**	10
30B	2750	**(−)-Nicotine**	7
32A	2511	**TC-2403**	26[6,35]
32B	691	**TC-1734**	11[7,35]

na, not active.

[a] Values are the average of three experiments. The assay-to-assay maximum variability in the series was ±3-fold. More common variability was ±2-fold.

Demethylation of nicotine analogs typically reduced affinity for the nicotinic receptors, but the extent of the reduction depended on the particular nicotine analog being examined.[31] *N*-Demethylation of compound **32B** decreased affinity by 4-fold (**30B**), however demethylation of compound **32A** increased the affinity by ca. 20-fold (**30A**), indicating a lack of bulk tolerance in this vicinity with respect to the *R*-isomer (**30A**).

The 6-fluoro substituted (*R*)-analog (**38A**) and its 6-chloro counterpart (**36A**) displayed comparable affinity (with respect to **30A**). The 6-bromo substituted (*R*)-analog (**37A**) and the 6-methoxy (*R*)-analog (**40**) displayed a decreased or negligible binding affinity, suggesting unfavorable interactions between the receptor and the ligand.

All active compounds were subsequently evaluated in an in vitro functional assay,[30] the best compounds being **(+)-51**[28b] and **30A**.[25b] Thus, the presence of agonist or partial agonist activity was detected by comparing the effects of compounds at 10 nM and 1 μM to the response elicited by 10 μM nicotine. In parallel, responses of test compounds were determined in the presence of the aspecific nicotine receptor antagonist mecamylamine, to exclude the involvement of other than nicotinergic mechanisms. Second, antagonist effects were assessed in a similar paradigm that measured the compounds' ability (10 μM) to inhibit the current evoked by 1 μM nicotine.

We found that compound **30A** was a partial agonist, displaying 62% of the in vitro efficacy of nicotine. In addition, compound **30A** blocked the nicotine response in vitro (70%). We found that compound **30A** has a favorable metabolic stability and brain penetration[25b] in spite of it modest oral availability. Thus, on the basis of its satisfactory binding affinity for the CNS nAChR and his partial agonistic activity in combination with its acceptable pharmacokinetics, we regard compound **30A** as a promising lead for the indications of cognition and smoking cessation.

Acknowledgment

Mr Jan Hoogendoorn is acknowledged for the chiral preparative HPLC separation of **18**, **24**, and **51**.

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16. Analytical data for (a); (*R*)-6-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**36A**): $[a]_D^{25} - 48$ (c1, toluene). 1H NMR (400 MHz, CDCl3): δ 11.0–10.0 (br s, 1H), 7.52 (d, $J = 8$ Hz, 1H), 7.01 (d, $J = 8$ Hz, 1H), 6.16 (s, 1H), 3.50–3.42 (m, 1H), 3.02–2.90 (m, 3H), 2.81–2.73 (m, 1H), 1.95–1.85 (m, 1H), 1.82–1.64 (m, 2H), 1.43–1.33 (m, 1H); (b) (*R*)-6-bromo-2-pyrrolidin-2-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridine (**37A**): $[a]_D^{25} - 50$ (c 1, toluene), which was converted to its (amorphous) salt (free base/fumaric acid (1:1)),[1]H NMR (400 MHz, DMSO-d_6): δ N_1–H invisible, 7.82 (d, $J = 8$ Hz, 1H), 7.18 (d, $J = 8$ Hz, 1H), 6.49 (s, 2H), 6.38 (s, 1H), 3.82–3.72 (m, 1H), 3.27–3.05 (m, 4H), 2.09–1.80 (m, 3H), 1.70–1.60 (m, 1H); (c) (*R*)-6-fluoro-2-pyrrolidin-2-ylmethyl-1*H*-pyrrolo[2,3-*b*]pyridine (**38A**): $[a]_D^{25} - 38$ (c1, toluene), which was converted to its (amorphous) salt (free base/fumaric acid (1:1)), ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2–11.7 (br s, 1H), 8.0 (br t, $J = 8$ Hz, 1H), 6.76 (br d, $J = 8$ Hz, 1H), 6.51 (s, 2H), 6.37 (s, 1H), 3.83–3.74 (m, 1H), 3.26–3.03 (m, 4H), 2.10–1.79 (m, 3H), 1.71–1.61 (m, 1H).
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23. Separation of the enantiomerically pure isomers was achieved using a chiral column (Chiralpak AD 20 μm, 250 × 4.6, MeOH/EtOH 1:1, 2 ml/min, $\delta = 220$ nm. Analytical data for **(+)-18**: R_t 5.6 min, $[a]_D^{25} + 4$ (c1, toluene). Analytical data for **(−)-18**: Rt 8.3 min, $[a]_D^{25} - 4$ (c1, toluene).
24. Separation of the enantiomerically pure isomers was achieved using a chiral column (Chiralpak AD-H 5 μm, 250 × 4.6, 100% EtOH + 0.1% diethylamine, 0.5 ml/min, $\delta = 220$ nm. Analytical data for **(−)-24**: R_t 18.4 min, $[a]_D^{25} - 10$ (c1, toluene). Analytical data for **(+)-24**: R_t 25.2 min, $[a]_D^{25} + 10$ (c1, toluene).
25. (a) Analytical data for **30A**: $[a]_D^{25} - 50$ (c1, toluene), which was reacted with 1 equiv of fumaric acid in EtOH and concentrated. Recrystallization from EtOH/ethyl acetate afforded a solid (free base/fumaric acid (1:1)), mp >163 °C (decomposition). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.7 (br s, 1H), 8.13 (dd, $J = 5$ Hz, 2 Hz, 1H), 7.84 (dd, $J = 8$ Hz, 2 Hz, 1H), 7.0 (dd, $J = 8$ Hz, 5 Hz, 1H), 6.51 (s, 2H), 6.32 (s, 1H), 3.85–3.77 (m, 1H), 3.26–3.04 (m, 4H), 2.09–1.80 (m, 3H), 1.71–1.61 (m, 1H).; (b) The *P*-glycoprotein transport factor[33] of the compound was also performed in vitro, being 1.2. Determination of the metabolic stability was performed in vitro (human liver homogenate[34]); $t_{1/2}$ being 266 min. Iv/po studies (rat) reveal a bioavailability of 11.3% and a brain-plasma ratio of 3.7. C_{max} following po administration was reached after 0.5–1 h with levels in brain of 280–290 ng/g and 70–120 ng/ml in plasma.

26. Analytical data for **32A**: $[a]_D^{25} + 44$ (c 1, toluene).
27. Analytical data for **40**: $[a]_D^{25} - 12$ (c 1, MeOH).
28. (a) Separation of the enantiomerically pure isomers was achieved using a chiral column (Chiralpak AD 20 μm, 250 × 4.6, 20% MeOH, 20% EtOH, 60% heptane, 2 ml/min, δ = 220 nm. Analytical data for **(−)-51**: R_t, 6.0 min, $[a]_D^{25} - 10$ (c1, MeOH). Analytical data for **(+)-51**: R_t 7.9 min, $[a]_D^{25} + 12$ (c1, MeOH). Both isomers were reacted with 1 equiv of fumaric acid in MeOH and concentrated to afford the salt of the title compound. Mp 130–133 °C (free base/fumaric acid (1:1.5)). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.7 (br s, 1H), 8.08 (dd, J = 5 Hz, 2 Hz, 1H), 7.78 (dd, J = 8 Hz, 2 Hz, 1H), 6.95 (dd, J = 8 Hz, 5 Hz, 1H), 6.4 (s, 3H), 6.27 (br s, 1H), 3.63–3.53 (m, 2H), 3.33–3.15 (m, 3H), 2.36–2.25 (m, 1H), 2.08–1.97 (m, 1H).; (b) Compound **(+)-51** was a full agonist, displaying the same in vitro efficacy as nicotine. The *P*-glycoprotein transport factor[33] for compound **(+)-51** was also determined in vitro, being 2. Determination of the metabolic stability was determined in vitro (human liver homogenate)[34]; $t_{1/2}$ being 134 min.
29. Affinity for neuronal nicotinic receptors was determined using rat brain membranes and [3H]cytisine at CEREP, by the receptor binding assay described by Pabreza et al.: '[3H]cytisine binding to nicotinic cholinergic receptors in brain' *Mol. Pharmacol*. **1991**, *39*, 9.
30. In vitro [3H]dopamine release. Dopamine release was measured using rat striatal slices, as described by Stoof et al. (*Brain Res.*, **1980**, *196*, 276). Test compounds or epibatidine was added together with the K+ pulse to the medium at t = 50 (10 nM) and t = 90 min (1 μM) for 5 min. In parallel, responses of test compound were determined in the presence of the aspecific nicotine receptor antagonist mecamylamine (0.1 μM) or the specific α4β2 *n*-acetylcholine receptor antagonist DHBE (1 μM). Effects of test compounds were calculated as percentages of the control group. Mecamylamine or DHBE sensitive release was expressed as percentage inhibition of evoked [3H]dopamine release in response to test compound. Within each assay, each test compound was replicated using 2–3 chambers; replicates were averaged.
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