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Ispronicline

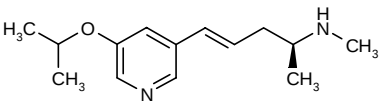
Rec INN; USAN

Nicotinic Acetylcholine α4β2 Agonist
Treatment of Cognition Disorders

AZD3480
TC-1734

5-(5-Isopropoxypyridin-3-yl)-*N*-methyl-4(*E*)-penten-2(*S*)-amine

InChI=1/C17H26/c1-5-15(4)8-6-9-16-10-7-11-17(13-16)12-14(2)3/h6-7,9-11,13-15H,5,8,12H2,1-4H3/b9-6+/t15-/m1/s1



$C_{14}H_{22}N_2O$
Mol wt: 234.3374

CAS: 252870-53-4

CAS: 482299-54-7

EN: 369309

Abstract

Ispronicline is a novel agonist at neuronal nicotinic acetylcholine α4β2 receptors (nAChRs), which are involved in cognition. It has little affinity for peripheral muscle or ganglionic nAChRs. A wide variety of preclinical tests assessing learning and memory have revealed ispronicline to have nootropic potential, to lack desensitization and to exert long-lasting effects on cognition when plasma levels would be minimal. Clinical studies have revealed it to improve cognition in volunteers and patients with mild cognitive impairment (MCI) and age-associated memory impairment (AAMI). Improvements were seen on a variety of cognitive measures and on selected features of the EEG. Further work is ongoing in patients with dementia and cognitive dysfunction in schizophrenia to further delineate its therapeutic potential.

Synthesis

Ispronicline can be synthesized as follows. The reaction of 3,5-dibromopyridine (I) with potassium isopropoxide (II) and powdered Cu in isopropanol at 140 °C gives 3-bromo-5-isopropoxypyridine (III), which is condensed with 4-penten-2(*R*)-ol (IV) by means of $Pd(OAc)_2$, TOTP and TEA in acetonitrile at 140 °C to yield [2(*R*),4(*E*)]-5-(5-isopropoxypyridin-3-yl)-4-penten-2-ol (V). The treatment of (V) with Ts-Cl in pyridine affords the corresponding tosylate (VI), which is finally treated with methylamine in ethanol/water to obtain the target secondary amine (1-4). Scheme 1.

Background

Memory impairment and deteriorating cognitive function arising from senile dementia or aging are increasingly prevalent. The worldwide prevalence of dementia is age-specific and ranges from 1% at 60-64 years to 45% at 95 years and over. The total worldwide societal cost of dementia in 2005 was estimated at USD 315 billion (5). Despite many therapeutic approaches, the mainstay of current therapy for Alzheimer's disease (AD) and dementia has targeted the cholinergic system via acetylcholinesterase (AChE) inhibitors, namely donepezil, rivastigmine and galantamine (6). The rationale for this approach stems from the fact that nicotinic agonists interact with neuronal nicotinic acetylcholine receptors (nAChRs), improving cognition in animal models and in the clinic (7). Moreover, neuronal nAChRs have been implicated in neuroprotection based on a large number of *in vitro* studies using a variety of chemical and hypoxic insults. One subtype, the α4β2 neuronal nAChR, is believed to be inhibited by very low concentrations of β-amyloid, the accumulation of which is thought to underlie the pathogenesis of AD (8).

Many nicotinic ligands have been developed for neuronal nAChRs (9, 10), but their lack of specificity meant that cardiovascular toxicity, emesis, seizures and hypothermia occurred at therapeutic doses. Moreover, desensitization eventually occurred, resulting in decreased efficacy over time. Ispronicline was developed to more closely approach the ideal nicotinic acetylcholine agonist in terms of efficacy and safety.

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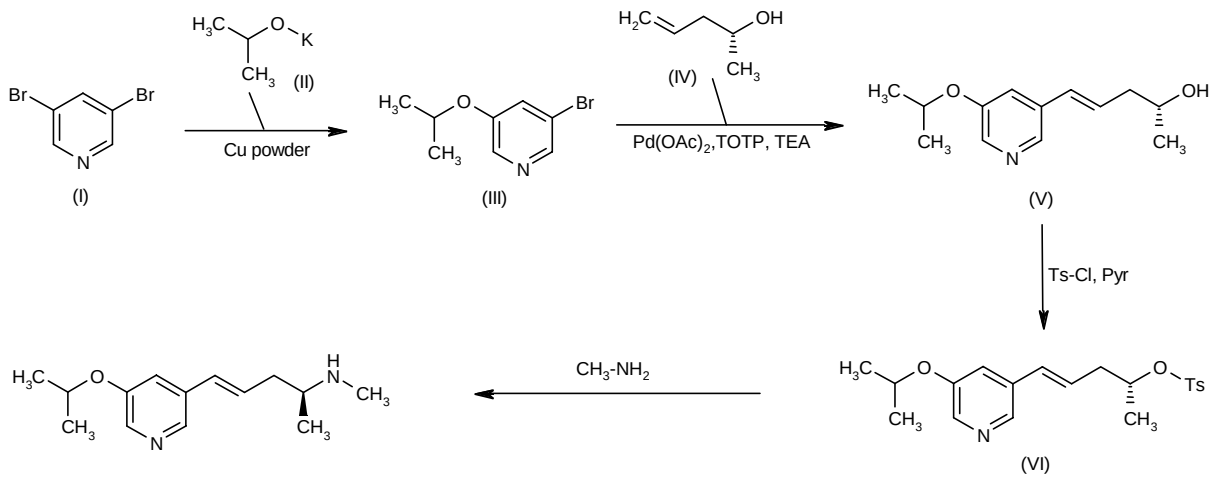
Scheme 1: Synthesis of Ispronicline



Preclinical Pharmacology

The key *in vitro* biochemical pharmacological profile of ispronicline is summarized and compared to that of nicotine in Table I. Ispronicline has an *in vitro* profile similar to that of nicotine in its affinity for $\alpha4\beta2$ neuronal nAChRs and dopamine (DA) release from the striatum, but differs markedly in its lack of affinity for peripheral nAChRs in the muscle and ganglia. Ispronicline at 0.1 μM was inactive on 135 receptor and enzyme systems, but at 10 μM it partially displaced binding at the $\alpha2$ (59%), imidazoline I2 (67%), peripheral muscarinic (60%), serotonin transporter (86%) and sigma 1 (88%) sites (11). Ispronicline was inactive on the $\alpha7$ receptor, which is believed to be involved in auditory gating deficits and cognition (7). In a separate study, (–)-nicotine itself was not a highly potent agonist at this receptor and the affinity of ispronicline appeared to be some 8-fold less (12).

Ispronicline is active in models assessing neuroprotection, *e.g.*, in reversing glutamate toxicity in rat forebrain neurons (11). Lactate dehydrogenase (LDH) release was used as a proxy measure of toxicity and this was inhibited by > 95% at 10 μM ispronicline. Nicotine (10 μM) produced a similar but less marked effect. In a more complex hypoxia/glucose deprivation model, ispronicline prevented the loss of synaptic transmission in rat hippocampal slices. The effect was concentration-dependent over the range 1-100 μM, with a 90% recovery rate at 100 μM; this was antagonized by 100 μM mecamylamine, implying that nAChR agonism was responsible.

Ispronicline dose-dependently (20-80 μmol/kg p.o.) increased ACh release in rat cerebral cortex after both acute and chronic (4-day) administration. This effect was also antagonized by mecamylamine (6 μmol/kg s.c.).

Table I: In vitro pharmacology of ispronicline (from Refs. 11 and 12).

	Ispronicline	Nicotine
Receptor affinities		
K_i $\alpha4\beta2$ (nM)	11	4
K_i $\alpha7$ (nM)	> 50,000	6290*
Functional activity		
Ion flux, thalamus: EC_{50}	220	591
E_{max}	57	87
DA release, striatum: EC_{50}	106	100
E_{max}	85	113
Muscle (% of E_{max}) at 100 μM	0	60
Ganglion (% of E_{max}) at 100 μM	0	60

E_{max}, maximal effect produced. *From Ref. 12.

There was no evidence that chronic administration led to tachyphylaxis (13), a finding echoed in ispronicline's effects on cognition (see below).

Standard animal models of learning and memory were used to define ispronicline's nootropic potential. Using the step-through passive avoidance test (11, 14) in rats, it was demonstrated that ispronicline (0.6, 1.0 and 3.0 μmol/kg s.c.) was able to reverse scopolamine-induced cognitive deficits. Moreover, when doses of AChE inhibitors that resulted in no detectable or significant effects were combined with similar submaximal doses of ispronicline, this resulted in significant effects on the reversal of scopolamine-induced memory loss.

The object recognition test (15) assesses the capacity to recognize an object presented on two occasions, some time apart. Memory is assessed as the relative time spent by a mouse exploring two objects, A and B, one

being familiar following a presentation 24 h previously (object A) and the other being new (object B). The time spent exploring each object was recorded. A recognition index (RI) was calculated for each animal and expressed as the ratio: [(Time B x 100)]/[Time A + Time B]. The RI is approximately 50% when animals do not remember (Time A and Time B are equivalent), and it is > 50% when the familiar object is remembered. The mean RI on vehicle, ispronicline 0.5 mg/kg and ispronicline 1 mg/kg p.o. was 45%, 55% and 72%, respectively, when measured 24 h after the training session. Moreover, pretreatment with mecamylamine (2.5 mg/kg i.p.) decreased RI in vehicle-treated mice when measured 3 h after the training period. After mecamylamine pretreatment, ispronicline (1 mg/kg p.o.) was unable to increase the RI 3 h post-training, although at this time ispronicline alone (1 mg/kg) showed an RI similar to that seen at 24 h (~72%). Therefore, nAChR function appears integral to memory formation in this test.

Ispronicline significantly improved both working and reference memory in the radial arm maze model after single doses of 0.1, 0.3, 0.6, 3 and 6 μmol/kg p.o. and after 6 days' treatment. Improvements in working memory were seen up to 18 h postdose (0.6 μmol/kg) (11). The ability of ispronicline to induce behavioral sensitization (increase in locomotor activity following chronic administration) was also examined. A 14-day treatment with 3 μmol/kg s.c. ispronicline did not increase hypermotility and was virtually indistinguishable from saline. In contrast, nicotine 3 μmol/kg s.c. produced hypermotility that was 300% greater than that of controls (or ispronicline) at 14 days.

At doses of 1 and 3 μmol/kg i.p. (but not at 10 μmol/kg i.p.) ispronicline was active in the Porsolt murine behavioral despair test. Imipramine (40 μmol/kg i.p.) was used as an active control; the effects of ispronicline were approximately 2-fold less than those of imipramine. An approximately 20-fold reduced propensity for dependence with ispronicline compared to nicotine was suggested by a drug discrimination test. Nicotine engaged appropriate responding in the majority (70%) of rats at 1.9 μmol/kg p.o. compared to a dose of 40 μmol/kg p.o. for ispronicline (11).

Pharmacokinetics and Metabolism

The major metabolites of ispronicline have been characterized as hydroxypyridyl, alkylcarboxyl, *N*-desalkylated, pyridine-*N*-oxide and glucuronidated hydroxypyridyl derivatives. The *N*-desalkylated (M3) metabolite is the only one detected in plasma that displays some affinity for the $\alpha4\beta2$ receptor, albeit some 40 times less than that of the parent drug (K_i = 462 nM) (11). Ispronicline is metabolized by cytochrome P-450 2D6, which is subject to genetic polymorphism and can lead to high individual differences in drug metabolic capacity (16).

The key pharmacokinetic parameters of ispronicline in rats and dogs are summarized in Table II. In both species, the parent drug was rapidly absorbed (t_{max}, or time to peak plasma concentrations = 0.25-2 h) and eliminated ($t_{1/2}$, or half-life = 0.8-2 h), and in the rat high brain concentrations were found at a t_{max} of 0.5-2 h. Total plasma clearance was markedly higher than hepatic blood flow in both species.

In two randomized, double-blind, placebo-controlled phase I studies in healthy male volunteers (16), the pharmacokinetic profile of oral ispronicline was investigated acutely in a single-dose study using doses of 2-320 mg and in a multiple-dose study using doses of 50, 100 and 200 mg/day over 21 days. The t_{max} was 1-3 h in both studies and the half-life ranged from 3 to 5.5 h after single doses and from 2.7 to 8.8 h after repeated doses. Renal excretion appeared to play a minor role in the drug's elimination, as was the case in rats and dogs. The key kinetic parameters for ispronicline and its major desalkylated metabolite (M3) are shown in Table III. As with ispronicline, the C_{max} and t_{max} increased with dose. The half-life ranges for ispronicline and the metabolite overlapped, implying that the latter was not responsible for the durability of the cognitive effects seen in animal and clinical studies.

Safety

Ispronicline was generally well tolerated. Phase I studies in volunteers showed that adverse events (AEs) were comparable in placebo and ispronicline subjects at single

Table II: Key pharmacokinetic parameters of oral and i.v. ispronicline in rats and dogs (from Ref. 11).

Parameter	Rat		Dog	
	oral	i.v.	oral	i.v.
C_{max} (ng/ml)	370	–	35	–
t_{max} (h)	0.25	–	0.5-2.0	–
V_d (l/kg)	–	4.6	–	6.2
$t_{1/2}$ (h)	1.1	0.8	1.3	2.0
Bioavailability (%)	73.3	–	31.4	–
Total plasma clearance (l/h/kg)	–	7.1	–	3.2
Hepatic/plasma blood flow (l/h/kg)	–	2.0/4.0	–	1.2/2.4
Cb_{max} (ng/g)	659	–	ND	ND

C_{max}, peak plasma concentration; t_{max}, time to peak plasma concentration; $t_{1/2}$, half-life; Cb_{max}, maximum brain concentration; ND, not determined.

Table III: Key pharmacokinetic parameters of oral ispronicline and its desalkylated metabolite (M3) (from Ref. 16).

Ispronicline dose (mg)	No. days administration	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{∞} (ng.h/ml)	CL_r (l/h)
50	1	10.35	2.0	2.9	48.3	11.7
	10	10.66	1.5	2.68	54.3	12.9
M3	1	1.30	2.0	4.0	10.2	NC
	10	1.40	2.5	3.8	9.8	NC
100	1	40.61	2.5	4.72	108.48	7.4
	10	68.03	1.5	6.58	172.30	7.6
M3	1	3.60	3.5	4.5	22.6	NC
	10	6.09	3.0	9.0	149.70	NC
200	1	110.18	1.4	4.71	627.33	5.1
	10	122.07	1.8	8.82	906.78	6.3
M3	1	9.3	2.9	5.9	57.7	NC
	10	13.7	3.0	6.7	145.8	NC

All values expressed as means except t_{max} (median); AUC_{∞}, area under the curve extrapolated to infinity; CL_r, renal clearance; NC, not calculated. Other abbreviations as in Table II.

doses up to 160 mg and repeated doses up to 200 mg. No clinically relevant changes were seen on hematological, biochemical or cardiovascular parameters. One subject experienced asymptomatic ventricular extrasystoles 17 h after a dose of 20 mg, which resolved spontaneously. The most frequently reported AE with acute dosing was mild to moderate headache (at 20-320 mg); with chronic dosing it was mild postural hypotension at 200 mg (16).

In elderly patients with age-associated memory impairment (AAMI), the commonest AEs were dizziness, headache and diarrhea. Dizziness was not accompanied by hypotension or other cardiovascular changes and was considered to be of cerebral origin. No relevant biochemical or hematological changes were seen in ispronicline or placebo patients (17).

Clinical Studies

In the same pharmacokinetic study described earlier (16) in volunteers, the cognitive performance and pharmaco-EEG profile of ispronicline were also examined (18). Different tasks were assessed and five factors –power and continuity of attention, quality of working and episodic memory and speed of memory– were derived from these tasks. After acute administration of 2-320 mg ispronicline, there were no relevant changes in these factors. Regarding EEG data, there were consistent acceleration changes in the α centroid and α peaks at 40-320 mg, with the largest changes occurring at 160-320 mg. These changes occurred 1-2 h postdose, consistent with the t_{max} values reported for ispronicline and its M3 metabolite. Repeated doses of 50, 100 or 200 mg increased several cognitive measures, although significant changes were only seen with 100- and 200-mg doses. Changes were seen on digit vigilance, word recall, picture recognition, power of attention and quality of episodic memory. The acceleration of the α centroid activity was confirmed in the repeated-dose study on both days 1 and 10 and was dose-related. An increase in mismatch negativity (MMN) and a reduction in MMN latency were seen, indicating an improvement in preattentional mechanisms.

A randomized, double-blind, placebo-controlled, crossover study in 6 healthy elderly volunteers (> 62 years) using a single dose of 80 mg ispronicline was conducted (19). Significant differences *versus* placebo were found on immediate and delayed recall, picture recognition and quality of episodic memory. These effects persisted for 36-48 h postdose (20).

Patients with mild cognitive impairment (MCI) or AAMI were investigated in four clinical studies of ispronicline. The key findings from these trials are summarized in Table IV.

A double-blind, placebo-controlled trial was conducted in 40 elderly subjects with MCI treated with 50 or 100 mg ispronicline for 3 weeks (21). The 50-mg dose was no different from placebo, whereas the 100-mg dose showed significant differences on power of attention and episodic memory, with trends on working memory and speed of memory.

Another double-blind, placebo-controlled study assessed the effects of placebo, 25 or 50 mg ispronicline once daily for 16 weeks in 193 patients with AAMI (aged 50-80 years) (22). Power and continuity of attention were significantly improved *versus* baseline at 25 mg, whereas 50 mg improved 4 of 5 of the measured parameters (Table IV). In a double-blind, placebo-controlled, crossover study in 76 elderly patients with AAMI, ascending oral doses of 50-150 mg ispronicline were given for 21 days (17). The 50-mg cohort showed statistical superiority over placebo on 4 of the 5 assessments (Table IV). At 150 mg (fed or fasted), 2 of the 5 factors (continuity and speed of memory) were superior to placebo. Only on speed of memory was placebo superior to ispronicline in the 100-mg group at a single time point. This study indicated that a plasma C_{max} range of 5-25/35 ng/ml was

Table IV: Key results from ispronicline trials in patients with MCI (mild cognitive impairment) and AAMI (age-associated memory impairment) (from Refs. 17, 21-23).

Condition/ reference	Dose groups (n)	Power of attention	Continuity of attention	Quality of episodic memory	Working memory	Speed of memory
MCI/20	50 mg (n=19)					
	100 mg (n=17)	$p = 0.042$		$p = 0.044$	*p = 0.070*	*p > 0.10*
AAMI/21	25 mg* (n=59)	$p = 0.0251$	$p = 0.028$			
	50 mg* (n=68)	$p = 0.0135$		$p = 0.028$	$p = 0.0013$	$p < 0.0019$
AAMI/16	50 mg (n=20)	$p = 0.001$	$p = 0.01$	$p = 0.019$		$p < 0.01$
	100 mg (n=20)			$p = 0.022$		$p = 0.033$
	125 mg (n=19)			*p = 0.08*	$p = 0.034$	$p = 0.048$
	150 mg fasted (n=5)	*p = 0.08*	$p = 0.049$		*p = 0.09*	$p = 0.018$
	150 mg fed (n=7)		$p = 0.028$	*p < 0.1*		$p = 0.046$
AAMI/22	50 mg (n=20)	$p < 0.05$**	$p < 0.05$**	$p < 0.05$**		$p < 0.05$**

*p values are *vs.* baseline; in other studies p values are *vs.* placebo. p values in italics are described as nearly significant (trend) by the authors. **Findings were described as 'statistically significant' in the abstract but the p value was not specified. The minimally statistically significant p value is thus stated.

associated with optimal benefit regarding cognitive effects. Another double-blind, placebo-controlled study in 20 elderly patients (> 60 years) with AAMI investigated the effects of 50 mg ispronicline once daily for 21 days (23). Positive effects were seen on the power and continuity of attention, quality of episodic secondary memory and speed of memory (Table IV).

Conclusions

Ispronicline is a novel neuronal nAChR $\alpha4\beta2$ agonist with little affinity for peripheral and ganglionic nAChRs and no affinity for a wide variety of other receptor and enzyme systems. Preclinical studies using different models exploring learning and memory revealed ispronicline to have nootropic potential. There was some evidence of antidepressant activity, yet to be confirmed in the clinic. Moreover, not only did desensitization not occur (as reported with nicotine), its effects on cognition were still evident when plasma levels of the parent drug would be negligible. This may be advantageous in the target population of MCI and AAMI patients, where missed doses may be commonly encountered. Alternate-day dosing may also be feasible.

The mismatch between pharmacodynamic and pharmacokinetic data may be due to changes in intracellular signaling or some impact on synaptic plasticity, or both, or other mechanisms (24). While the optimal clinical dose regimen of ispronicline in MCI and AAMI patients remains to be determined, it appears that doses of 50-80 mg/day significantly improve the majority of cognitive factors assessed.

Ispronicline appears to be well tolerated and few patients withdrew due to AEs. Further work with long-term treatment will be necessary, in addition to studies comparing it to or combining it with AChE inhibitors. Indeed, one 12-week comparative study with donepezil in AD is ongoing (25). It will be interesting to see how ispronicline's effects on cognition compare with varenicline, a marketed $\alpha4\beta2$ partial agonist with full agonist activity at $\alpha7$ receptors (12). This drug's effects on cognition are currently being assessed in schizophrenia patients with cognitive dysfunction (26), as are those of ispronicline (27).

Sources

Targacept, Inc. (US); developed in collaboration with AstraZeneca.

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