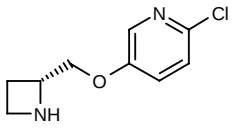
Drugs of the Future 2001, 26(10): 927-934

CCC: 0377-8282/2001

ABT-594

Treatment of Neuropathic Pain
Nicotinic Agonist

(*R*)-2-Chloro-5-(2-azetidinylmethoxy)pyridine



$C_9H_{11}ClN_2O$ Mol wt: 198.6519

CAS: 198283-73-7
CAS: 203564-54-9 (as monohydrochloride)
CAS: 209326-19-2 (as dihydrochloride)
CAS: 209326-18-1 (as monobenzoate salt)
CAS: 198283-74-8 (as monotosylate salt)

EN: 258695

Synthesis

ABT-594 can be prepared by several similar ways: Scheme 1.

Cyclization of D-aspartic acid dibenzyl ester by means of TMS-Cl, TEA and *tert*-butylmagnesium chloride in dichloromethane gives the azetidinone (II), which is reduced with $LiAlH_4$ in THF to yield the azetidinemethanol (III). Protection of the NH group of (III) with Boc_2O in THF affords the carbamate (IV) (1-3), which is treated with Ms-Cl and TEA in THF to provide mesylate (V). Condensation of compound (V) with 2-chloro-5-hydroxypyridine (VI) by means of KOH in hot DMF gives the *N*-protected adduct (VII), which is finally deprotected with TsOH or TFA (1).

Alternatively, Mitsunobu coupling of carbinol (IV) with pyridine (VI) by means of PPh_3 and DEAD in THF affords the already reported *N*-protected adduct (VII) (4).

Alternatively, carbinol (IV) can be treated with Ts-Cl instead of Ms-Cl, and the resulting tosylate (VIII) condensed with the pyridine (VI) by means of KOH in hot DMF to yield the already reported *N*-protected adduct (VII) (2, 3).

The intermediate 1-(*tert*-butoxycarbonyl)-azetidine-2-methanol (IV) can also be obtained by deprotection of 1-(benzyloxycarbonyl)azetidine-2(*R*)-carboxylic acid (IX) with H_2 over Pd/C in methanol to give the free azetidine (X), reprotection of (X) with Boc_2O and DIEA in dioxane/water to yield 1-(*tert*-butoxycarbonyl)azetidine-2(*R*)-carboxylic acid (XI) and finally reduction of (XI) to carbinol (IV) by means of BH_3 in THF (4).

The intermediate 2-chloro-5-hydroxypyridine (VI) can be obtained by three different ways:

a) The reaction of 5-amino-2-chloropyridine (XII) with *tert*-butyl nitrite and BF_3/Et_2O in dichloromethane/DME, followed by acylation with hot Ac_2O gives the acetoxypyridine (XIII), which is hydrolyzed with K_2CO_3 in methanol to yield the target intermediate (VI) (1-3).

b) The reaction of 5-amino-2-chloropyridine (XII) with $NaNO_2$ in acidic medium under Effenberger conditions directly yields the target intermediate (VI) (4).

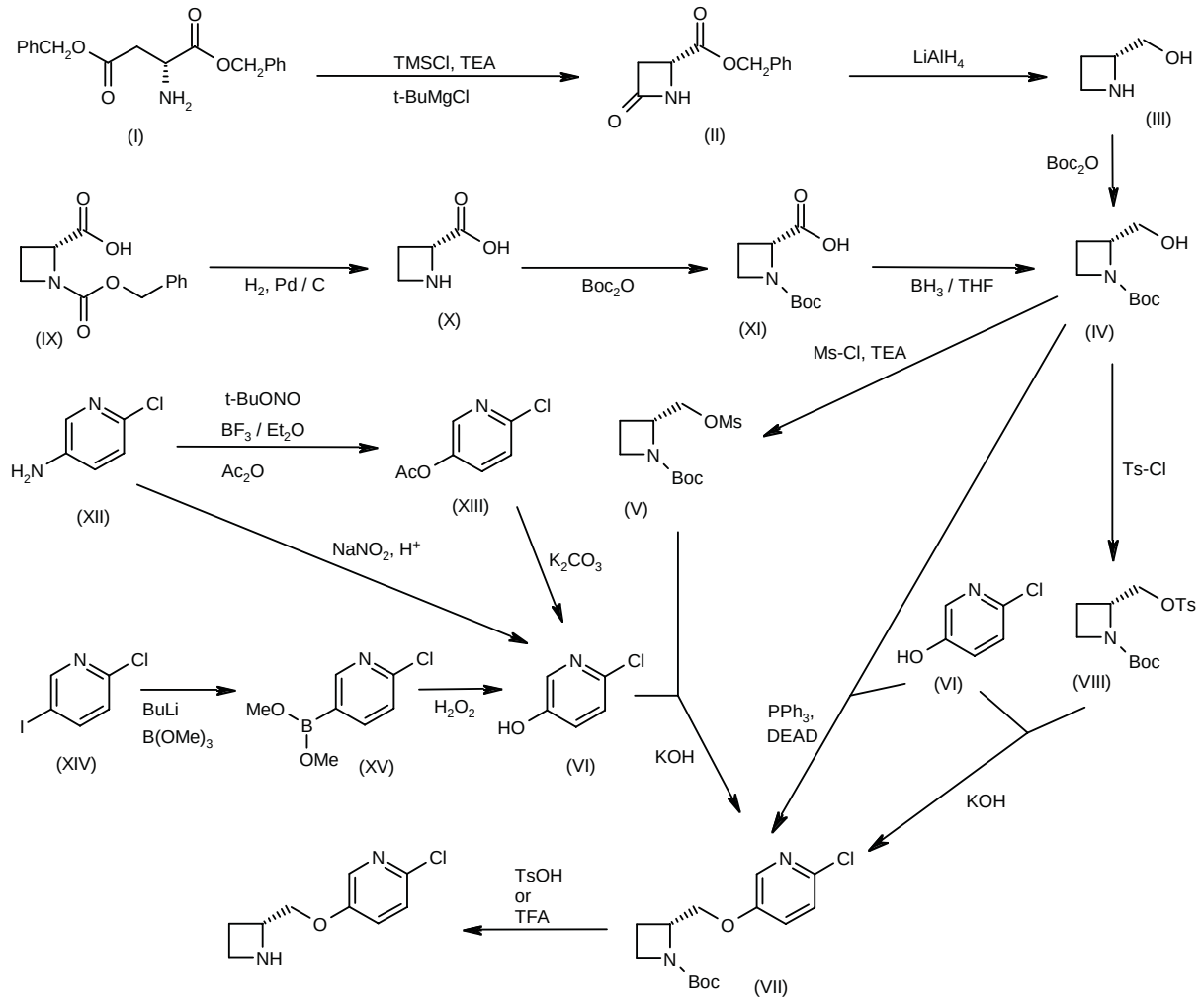
c) The reaction of 2-chloro-5-iodopyridine (XIV) with BuLi and $B(OMe)_3$ in THF gives the boronate (XV), which is oxidized with H_2O_2 in acetic acid to afford the target intermediate (VI) (5).

Introduction

The sensation of pain indicates harm or impending danger to body tissues and necessitates the need to avoid injury. Pain involves both sensory and emotional aspects. When it occurs during injury or illness and resolves with time, it is defined as acute. However, when it persists for longer than 6 months, it is considered chronic. Chronic pain can be characterized as pain resulting from ongoing tissue damage such as in the case of cancer or osteoarthritis. However, pain may also be present and persist long after resolution of tissue damage or in the absence of causative illness or injury. This type of chronic pain results from the continued transmission of pain signals by the nervous system and, in this case, pain becomes the pathological condition in place of the predisposing condition. Chronic pain is estimated to be experienced by hundreds of millions of individuals worldwide and the American Association of Neurological Surgeons reported that 75-80 million Americans suffer from chronic pain (5).

L.A. Sorbera, L. Revel, P.A. Leeson, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of ABT-594

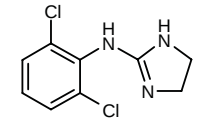


Neuropathic (or neurogenic) pain is one type of chronic pain that persists long after imminent or actual tissue damage. Several subtypes of neuropathic pain exist, including such conditions as diabetic neuropathy, AIDS neuropathy and carpal tunnel syndrome. Individuals may experience polyneuropathy where several nerves are involved or mononeuropathy where only 1 nerve is involved. Symptoms can range from mild tingling and numbness to searing, incapacitating pain. Neuropathy is due to damage to peripheral nerves between the brain and muscles, skin, internal organs and blood vessels that can be caused by several factors including diabetes, autoimmune disease, repetitive stress, toxic chemicals, alcohol abuse and some medications. Damage to peripheral nerves interferes with normal neuronal signal transduction and can result in loss of normal sensations and/or movement. Damage to sensory nerves manifests as numbness, tingling and/or pain. Individuals suffering from neuropathic pain do not respond well to standard therapies such as opioids, NSAIDs or other traditional analgesics (6). As a result, research has focused on developing compounds with alternative mechanisms of action. Some of these agents are shown in Table I (6).

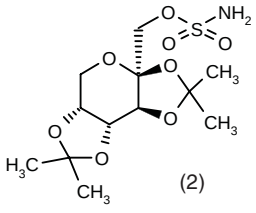
One such novel target for the treatment of neuropathic pain are the nicotinic acetylcholine receptors (nAChRs). These receptors are composed of 5 protein subunits arranged around a central pore thus forming a ligand-gated ion channel. Eleven neuronal nAChR subunits ($\alpha_{2\text{-}9}$ and $\beta_{2\text{-}4}$) have been described so far. Although the stochiometry of most brain nAChRs have not yet been elucidated, abundant forms include $\alpha_4\beta_2$ nAChR, thought to be composed of 2 α_4 and 3 β_2 subunits, and the homooligomer, α_7; other more complex receptors have also been identified in the brain (*e.g.*,

Table I: Drugs in development for the treatment of neuropathic pain (Prous Science Integrity database).

Drug Name	Originator/Licensee	Mechanism of Action	Status
1. Clonidine*	Curatek	α_2-Adrenoceptor agonist	Phase III
2. Topiramate**	R.W. Johnson		Phase III
3. Ziconotide	Elan	N-type neuronal calcium channel blocker	Phase III
4. ABT-594	Abbott	Nicotinic acetylcholine receptor agonist	Phase II
5. Capsavanil	Korea Res. Inst. Chem. Technol./Dong-A	Capsaicin analogue, vanilloid receptor antagonist	Phase II
6. CJC-1008+	ConjuChem	Opioid analgesic	Phase II
7. CNS-5161	Cambridge Neuroscience	NMDA antagonist	Phase II
8. Emfilermin	Amrad		Phase II
9. Harkoseride	Schwarz	NMDA glycine-site antagonist	Phase II
10. Lamotrigine**	GlaxoSmithKline	Glutamate release inhibitor	Phase II
11. Prosaptide TX14(A)	Bio-Technology General	Neuotrophic peptide	Phase II
12. Rufinamide	Novartis	Sodium channel blocker	Phase II
13. NNC-05-1869	Novo Nordisk/ReNeuron	Histamine H_1 receptor antagonist	Phase II
14. Resiniferatoxin	NIH/Afferon/Mundipharma	Capsaicin analogue, vanilloid receptor antagonist	Phase I/II
15. CT-3++	Atlantic Technology Ventures	Cannabinoid	Preclinical



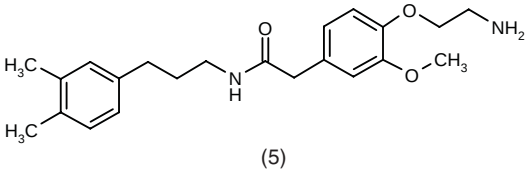
(1)



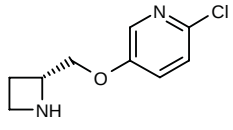
(2)

H-Cys-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH_2 cyclic *S*-3.1-*S*-3.16:*S*-3.8-*S*-3.20:*S*-3-15-*S*-3.25-tris(disulfide)

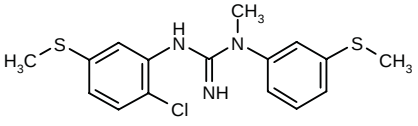
(3)



(5)



(4)



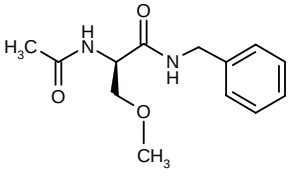
(7)

Leukemia-inhibiting factor (human)

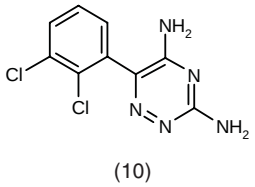
(8)

H-Thr-D-Ala-Leu-Ile-Asp-Asn-Asn-Ala-Thr-Glu-Glu-Ile-Leu-Tyr-OH

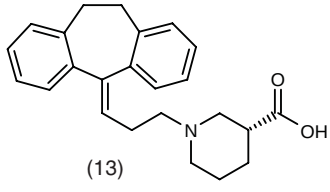
(11)



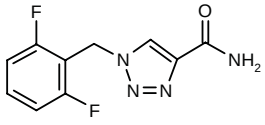
(9)



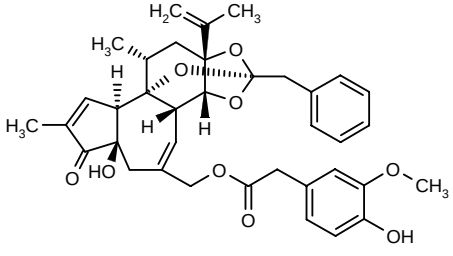
(10)



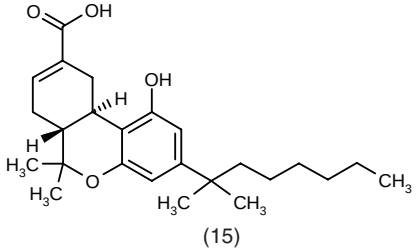
(13)



(12)



(14)

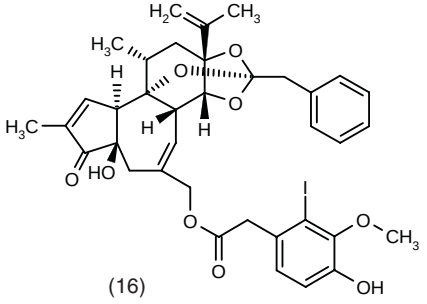


(15)

Continued

Table I (Cont.): Drugs in development for the treatment of neuropathic pain (Prous Science Integrity database).

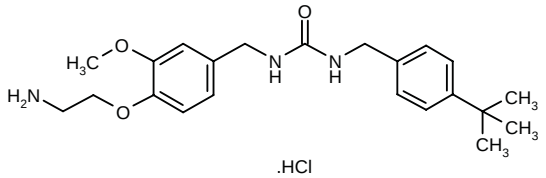
Drug Name	Originator/Licensee	Mechanism of Action	Status
16. Iodo-resiniferatoxin	Novo Nordisk	Capsaicin analogue, vanilloid receptor antagonist	Preclinical
17. NW-1029+	Newron	Sodium channel blocker	Preclinical
18. ReN-0189+	Novo Nordisk/ReNeuron	Neurin compound that acts on C-nociceptors	Preclinical
19. SDZ-249-665	Novartis	Capsaicin analogue, vanilloid receptor antagonist	Preclinical
20. Substance P-saporin	Vanderbilt Univ.		Preclinical
21. Zoledronic acid***	Novartis	Bisphosphonate	Preclinical



(16)

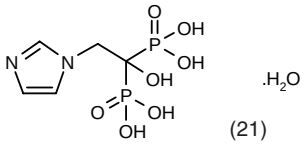
Conjugate of substance P and the ribosome-inactivating protein saporin

(20)



.HCl

(19)



.H_2O

(21)

*Marketed for arterial hypertension. **Marketed for epilepsy. ***Marketed for tumor-induced hypercalcemia. +Structure not yet detected. ++In combination with opioids.

$\alpha_3\beta_2\beta_4\alpha_5$). Neuromuscular nAChRs in skeletal muscle are distinct from nAChR found in the CNS and are composed of 2 α subunits and 1 β, γ (or ε) and δ subunit (7).

The function of the various nAChR subunits continues to be the subject of intense investigation. It has been demonstrated in animal studies that the α_4 subunit of nAChR is required for the antinociceptive actions of nicotine and nicotinic agonists. Nicotine was reported early on to have antinociceptive activity but due to its nonselectivity for nAChR subtypes and its low safety profile, it has never been developed (8-11). Thus, the search for nicotinic agonists was initiated. One such nicotinic agonist is epibatidine, an alkaloid isolated from the skin of the Ecuadorian frog, *Epipedobactes tricolor* (12). Epibatidine was found to be a potent nAChR agonist demonstrating analgesic activity that was 100-200 times more potent than morphine (13). However, epibatidine is a nonselective nAChR agonist with full agonist activity observed at $\alpha_2\beta_2$, $\alpha_3\beta_2$, $\alpha_3\beta_4$, α_7 and α_8 nAChRs. As a results, the agent possesses a limited therapeutic index due to its adverse effects on CNS responses and respiratory, gastrointestinal and cardiovascular function. Thus, research has became focused on developing compounds selective for specific nAChR subtypes. In contrast, ABT-594, a 3-pyridyl ether, has shown potent analgesic activity (40- to 100-fold more potent than morphine). Although it is a full agonist at neuronal $\alpha_4\beta_2$, α_7 and $\alpha\beta\delta\gamma$ nAChR subtypes, it has shown enhanced selectivity for the $\alpha_4\beta_2$ subtype (4, 14). ABT-594 has been selected for further development as a treatment for neuropathic pain.

Pharmacological Actions

In vitro *studies*

ABT-594 showed high affinity binding for recombinant human $\alpha_4\beta_2$ nAChR expressed in HEK cells (K_i = 0.055 nM) and the rat $\alpha_4\beta_2$ nAChR in rat brain membranes (K_i = 0.037 nM) in experiments examining displacement of [^{3}H]-cysteine binding. In contrast, the agent showed significantly less activity in competitively displacing [^{125}I]α-bungarotoxin from α-bungarotoxin-sensitive nAChR in brain (K_i = 12,800 nM for the α_7 subtype) and at neuromuscular junctions (K_i = 10,000 nM at the $\alpha_1\beta_1\gamma\delta$ subtype) using *Torpedo californica* electroplax membranes. Similarly, ABT-594 was less potent than (±)-epibatidine and only slightly more potent than (–)-nicotine in evoking currents from human α_7 homomeric nAChRs expressed in *Xenopus* oocytes. Moreover, ABT-594 exhibited low affinity (K_i > 1000 nM) for other targets including other ligand-gated ion channels, heterotrimeric GTP-binding protein-coupled opioid and muscarinic receptors, amine uptake sites, channel proteins, second messenger proteins and cyclooxygenase isoforms (14, 15).

When compared to (±)-epibatidine, ABT-594 had 20-fold less affinity for α_3-containing nAChR expressed in human sympathetic ganglion-like cells (IMR-32).

ABT-594 was more than 30-fold more potent than (–)-nicotine (EC_{50} = 140 ± 16 nM *vs.* 4.2 ± 1.1 μM; intrinsic activity [IA] = 130 *vs.* 100%) in a Ca^{2+} flux assay (*i.e.*, $^{86}Rb^{+}$ efflux) using human $\alpha_4\beta_2$ nAChR expressed in K177 cells; the nAChR antagonist mecamylamine (100 μM) attenuated the responses of both compounds (15).

In experiments using rat dorsal spinal cord slices as *in vitro* model of primary afferent pain fiber (*i.e.*, C fibers) activation which is known to be modulated by nAChRs, ABT-594 (1-30 μM) dose-dependently inhibited capsaicin-induced release of 2 neuropeptides associated with pain transmission, substance P and calcitonin gene related peptide (CGRP); this effect was blocked by mecamylamine. Results suggest that the antinociceptive effects of ABT-594 may be via modulation of substance P and CGRP release (15).

In vivo *studies*

The antinociceptive effects of ABT-594 have been demonstrated in a number of *in vivo* models. The agent was shown to be effective against both acute noxious stimuli (*i.e.*, hot- and cold-plate tests) and persistent visceral irritation (*i.e.*, writhing assay) in mice. Administration of the agent (i.p. or p.o.) dose-dependently increased jump latencies in the hot-plate test; the agent was 10-fold more potent when administered i.p. Significant effects were noted with a dose of 0.62 μmol/kg i.p. as compared to 19 μmol/kg i.p. for (–)-nicotine. The effects of ABT-594 were sustained for at least 1 h and blocked by pretreatment with mecamylamine but not naltrexone, an opioid receptor antagonist, indicating that the effects of the agent were via activation of nAChR and not μ-opioid receptors. Similar results were obtained for the cold-plate assay. ABT-594 (0.19 and 0.62 μmol/kg i.p. 30 min before giving the chemical irritant, phenyl-*p*-quinone) was also effective against persistent visceral pain since it significantly decreased the number of animals responding to phenyl-*p*-quinone (68 μmol/kg i.p.). Results from this study also showed that treatment with the agent did not impair motor coordination in the rotarod test but decreased body temperature and spontaneous exploration. Moreover, ABT-594 (0.019 and 0.062 μmol/kg i.p.) induced anxiolytic-like activity (*e.g.*, increased exploration in the open arms) in the elevated plus-maze test. The agent prolonged ethanol- and pentobarbital-induced hypnotic effects but did not influence pentobarbital-induced lethality. Safety results indicated that EC_{50} and LD_{50} values for overt seizure production were 10 and 100 times the dose required for minimal effective antinociceptive effects (16).

The antinociceptive effects of ABT-594 were further demonstrated in studies using rats. Results similar to those obtained in mice were obtained in the hot-plate test where response latencies were prolonged following ABT-594 administration (0.05 and 0.1 mg/kg s.c.). However, unlike (–)-nicotine and (±)-epibatidine, ABT-594 had no effect on rotarod impairment although hypothermia and life-threatening seizures were observed with treatment. ABT-594 (0.01 and 0.1 mg/kg i.v.) also increased blood pressure in a manner similar to the effects observed with both (–)-nicotine (0.03, 0.1 and 0.3 mg/kg i.v.) and (±)-epibatidine (0.001 and 0.003 mg/kg i.v.). Pretreatment with mecamylamine (1 mg/kg s.c. or i.v.) blocked ABT-594-induced antinociceptive effects in addition to seizures and hypertension. Further multiple-dose studies in which rats were administered ABT-594 (0.2 mg/kg/day s.c. continuous infusion) for 7 days followed by a mecamylamine (1 mg/kg i.p.) challenge revealed that the agent induced a nicotine-like abstinence syndrome, indicating that it may possess a liability for nicotine-like dependence (17). On the other hand, data obtained in rats have indicated that ABT-594, unlike morphine, does not induce opioid-like withdrawal effects at discontinuation of treatment, thus indicating a lack of liability for physical dependence. Moreover, the reduction in gastric motility observed in rats following morphine administration was not observed with ABT-594 treatment (14).

Although ABT-594 was dose-dependently effective in the tail-flick test, the effects of the agent (10-300 μg/kg s.c.) and (±)-epibatidine (0.3-10 μg/kg s.c.) were only seen at high doses that also caused a disruption in performance in the rotarod test. In contrast, ABT-594 given at lower doses (3-100 μg/kg s.c.) significantly and dose-dependently reversed hyperalgesia induced by injection of Freund's complete adjuvant into the left hind paw (maximal reversal = 55.0 ± 6.1% with 100 μg/kg seen 1 h postdosing) and neuropathic hyperalgesia induced by partial ligation of the left sciatic nerve for 11-15 days (maximum reversal = 59.3 ± 7.5% with 100 μg/kg seen 1 h postdosing) (18).

The preclinical efficacy of ABT-594 against acute thermal (*i.e.*, hot box test) and persistent chemical (*i.e.*, formalin test) pain was also shown in rats. Significant and dose-dependent antinociceptive responses were observed following administration of ABT-594 at doses of 0.03, 0.1 and 0.3 μmol/kg i.p. The effects of ABT-594 were found to be sustained following 5-day multiple dosing (b.i.d. i.p.). Significant antinociceptive responses were also observed in the formalin test where the agent (0.1 and 0.3 μmol/kg i.p. or p.o. 5 min prior to formalin injection) attenuated formalin (5% s.c. into a rear paw)-induced nociceptive responses at both 0-10 min and 30-50 min after formalin injection. Treatment with mecamylamine (1.5 mcg/mol i.p. 15 min before ABT-594) or chlorisondamine (10 μg/rat i.c.v. for 5 days prior to testing), another nAChR antagonist, reversed the effects of ABT-594 in both the hot-plate and formalin tests; pretreatment with naltrexone (2.65 μmol/kg i.p.) had no effect (19).

Further results showed that although acute ABT-594 treatment (0.03 and 0.3 μmol/lg i.p.) initially reduced vertical and horizontal open-field locomotor activity in rats, this effect was not seen in animals dosed repeatedly b.i.d. for 5 days. Acute treatment with the agent (0.36 μmol/kg i.p.) also reduced motor coordination as

assessed by the time rats could maintain balance in an edge-balance test. Body temperature was also decreased with ABT-594 treatment. However, once again, repeated dosing eliminated these effects of ABT-594 without affecting the agent's antinociceptive efficacy. Acute oral dosing was found to attenuate the effects of i.p. administered ABT-594 on motor activity. In this study, ABT-594 (0.03-0.3 μmol/kg i.p.) was also shown to activate free-running EEG in a manner similar to caffeine (50 μmol/kg i.p.) but in contrast to morphine (42 μmol/kg i.p.) which produced sedative-like effects (19).

ABT-594 was also effective against nerve ligation (*i.e.*, the Chung model; ligation of spinal nerves L5 and L6) and diabetic (streptozotocin [STZ; 80 mg/kg i.p.) neuropathy in rats. In the Chung model which assessed tactile allodynia, significant and comparable antiallodynic effects were observed following both oral (0.1-1 μmol/kg) and i.p. (0.3 μmol/kg) dosing. When compared to the effects of repeated-dose morphine (21 μmol/kg b.i.d. i.p. for 5 days), repeated-dose ABT-594 (0.3 μmol/kg b.i.d. i.p. for 5 days) continued to show antiallodynic efficacy while the effects of morphine were significantly decreased. Moreover, in the STZ diabetic rat model, although morphine was ineffective, ABT-594 (0.3 μmol/kg i.p.) decreased mechanical hyperalgesia as assessed by pressure applied to the dorsal surface of the rear paw (20).

Results from a study in rats demonstrated that the antinociceptive effects of ABT-594 may involve activation of the nucleus raphe magnus, thus implicating a critical descending pain-inhibitory mechanism. Administration of ABT-594 (0.03, 0.1 and 0.3 μmol/kg i.p.) induced dose-dependent expression of Fos protein in the nucleus raphe magnus, an area of the brain which shows expression of α_4-containing nAChRs on serotonergic neurons. The effect was blocked following pretreatment with mecamylamine (5 μmol/kg i.p.) but not with the peripheral nAChR antagonist, hexamethonium (15 μmol/kg i.p.) (21).

In addition to its antinociceptive effects, ABT-594 has also been shown to exhibit other important effects. For example, the antiinflammatory efficacy of ABT-594 was demonstrated in a study using a rat carrageenan paw edema model of acute inflammation. ABT-594 potently inhibited edema (ED_{30} = 0.05 mg/kg i.p.) with an efficacy 86% that of dexamethasone. A maximum effect of 74% inhibition of edema was observed with an ABT-594 dose of 0.3 mg/kg i.p. at 2 h postdosing. The activity of the agent significantly decreased thereafter, with 38% inhibition observed for the remainder of the 7-h testing period. Since mecamylamine blocked the effects of ABT-594 in this model and the agent showed similar efficacy in both normal and adrenalectomized rats indicating a mechanism of action independent of adrenal steroid or epinephrine release, it was concluded that the antiedmatous effects of ABT-594 were via activation of nAChR. Multiple ABT-594 dosing (b.i.d. i.p. for 5 days) resulted in a significant reduction in inhibition of edema from 86% to 59% (22)

ABT-594 may also possess neuroprotective properties and therefore may afford therapeutic efficacy in the treatment of Alzheimer's and Parkinson's diseases. ABT-594 (0.15, 0.3 and 6 μmol/kg i.p.) treatment significantly and dose-dependently increased fibroblast growth factor-2 (FGF-2) mRNA in the frontoparietal cerebral cortex, hippocampal formation, striatum and substantia nigra 4 h postdosing. Expression of FGF-1, BDNF, NGF, NT-4, GDNF and FGF receptors 1, 2 or 3 were unaffected by treatment. The upregulation of FGF-2 expression occurred in both neuronal and nonneuronal cells and effects were antagonized by pretreatment (4 mg/kg 15 min before ABT-594) with dihydro-betaerythroidine, a preferential $\alpha_4\beta_2$ antagonist (23).

Pharmacokinetics

The pharmacokinetics of ABT-594 were examined in CD-1 mice (200 nmol/kg), rats (300 nmol/kg), beagles (20 and 100 nmol/kg i.v. and p.o., respectively) and cynomolgus monkey (20 and 100 nmol/kg i.v. and p.o., respectively). The agent exhibited a short plasma elimination half-life of less than 0.5 h and rapid clearance from plasma (4 l·h/kg). A 4-fold longer half-life was seen for rats and monkeys as compared to mice although the longest $t_{1/2}$ was observed in dogs (4.7 h). In all species except monkey, oral ABT-594 was rapidly absorbed with peak plasma concentrations of the agent seen within 90 min. In contrast, absorption was slower in monkeys with peak plasma concentrations observed 2.2 h postdosing. Oral bioavailability for mouse, rat, monkey and dog were 78, 61, 80 and 35%, respectively (24).

Following oral or i.p. dosing, ABT-594 peak concentrations and AUC values were 2-fold higher in the brain and spinal cord as compared to plasma. Brain to plasma ratios of 2.5, 1.5, 2 and 2 were obtained for forebrain, cerebellum, brainstem and spinal cord, respectively. Half-life values were similar to those obtained in plasma (1.5 and 2.5 h for i.p. and p.o. routes, respectively) (24).

Results from radiotracer experiments performed in rats showed that ABT-594 (p.o. and i.v.) was excreted predominantly unchanged in urine; 91.5 and 89.1% of the dose was excreted in urine within 3 days of p.o. and i.v. dosing, respectively, and 4% of the dose was recovered in feces after both i.v. and p.o. dosing. Up to 8 possible metabolites were identified in plasma, urine, feces and/or bile. Similarly, several metabolites have been detected in metabolism experiments using liver slices from rats, dogs, monkeys and humans. Results from these studies also showed that the apparent rate of metabolism of the agent was approximately 4-fold faster in liver preparations from dogs and monkeys as compared to rats and humans (24).

Clinical Studies

ABT-594 in currently undergoing phase II trials as a treatment for neuropathic and chronic pain (25, 26).

Manufacturer

Abbott Laboratories, Inc. (US).

References

1. Lynch, J.K., Holladay, M.W., Ryther, K.B., Bai, H., Hsiao, C.-N., Morton, H.E., Dickman, D.A., Arnold, W., King, S.A. *Efficient asymmetric synthesis of ABT-594, a potent, orally effective analgesic.* Tetrahedron Asymmetry 1998, 9: 2791-4.

2. Holladay, M.W., Arnric, S.P., Bai, H., Dart, M.J., Lin, N.-H., Lynch, J.K., Ryther, K.B., Sullivan, J.P., Wasicak, J.T., Ehrlich, P.P. (Abbott Laboratories Inc.). *3-Pyridyl enantiomers and their use as analgesics.* EP 0950057, JP 2001504857, WO 9825920.

3. Holladay, M.W., Abreo, M.A., Gunn, D.E., Lin, N.-H., Garvey, D.S., Ryther, K., Lebold, S.A., Elliott, R.L., He, Y., Wasiak, J.T., Bai, H., Dart, M.J., Ehrlich, P.P., Li, Y., Kincaid, J.F., Schkeryantz, J.M., Lynch, J.K. (Abbott Laboratories Inc.). *Heterocyclic ether and thioether cpds. useful in controlling chemical synaptic transmission.* EP 1047690, WO 9932480.

4. Holladay, M.W., Wasicak, J.T., Lin, N.-H. et al. *Identification and initial structure-activity relationships of (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594), a potent, orally active, non-opiate analgesic agent acting via neuronal nicotinic acetylcholine receptors.* J Med Chem 1998, 41: 407-12.

5. Krow, G.R., Xiao, Y., Cannon, K., Swan, S.A., Nickel, A. *An alternative synthesis of 2-chloro-5-hydroxypyridine: A key component of the non-opioid analgesic agent ABT-594.* Synth Commun 2000, 30: 4093-6.

6. Prous Science R&D Backgrounders: *Pain (online publication).* Updated July 6, 2001.

7. Lloyd, G.K., Williams, M. *Neuronal nicotinic acetylcholine receptors as novel drug targets.* J Pharmacol Exp Ther 2000, 292: 461-7.

8. Davis, L., Pollock, L.J., Stone, T.T. *Visceral pain.* Surg Gynecol Obstet 1932, 55: 418-27.

9. Qian, C., Li, T., Shen, T.Y., Libertine-Garahan, L., Eckman, J., Biftu, T., Ip, S. *Epibatidine is a nicotinic analgesic.* Eur J Pharmacol 1993, 250: R13-4.

10. Caggiula, A.R., Epstein, L.H., Perkins, K.A., Saylor, S. *Different methods of assessing nicotine-induced antinociception may engage different neural mechanisms.* Psychopharmacology 1995, 122: 301-6.

11. Benowitz, N.L. *Nicotine and coronary heart disease.* Trends Cardiovasc Med 1992, 1: 315-21.

12. Spande, T.F., Garraffo, H.M., Edwards, M.W., Yeh, H.J.C., Pannell, L., Daly, J.W. *A new class of alkaloids from a dendrobatid poison frog: A structure for alkaloid 251F.* J Am Chem Soc 1992, 114: 3475-8.

13. Badio, B., Daly, J.W. *Epibatidine, a potent analgetic and nicotinic agonist.* Mol Pharmacol 1994, 45: 563-9.

14. Bannon, A.W., Decker, M.W., Holladay, M.W. et al. *Broad-spectrum, non-opioid analgesic activity by selective modulation of neuronal nicotinic acetylcholine receptors.* Science 1998, 279: 77-81.

15. Donnelly-Roberts, D.L., Puttfarcken, P.S., Kuntzweiler, T.A. et al. *ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine]: A novel, orally effective analgesic acting via neuronal nicotinic acetylcholine receptors: I. In vitro characterization.* J Pharmacol Exp Ther 1998, 285: 777-86.

16. Decker, M.W., Bannon, A.W., Buckley, M.J., Kim, D.J., Holladay, M.W., Ryther, K.B., Lin, N.H., Wasicak, J.T., Williams, M., Arneric, S.P. *Antinociceptive effects of the novel neuronal nicotinic acetylcholine receptor agonist, ABT-594, in mice.* Eur J Pharmacol 1998, 346: 23-33.

17. Boyce, S., Webb, J.K., Shepheard, S.L., Russell, M.G., Hill, R.G., Rupniak, N.M. *Analgesic and toxic effects of ABT-594 resemble epibatidine and nicotine in rats.* Pain 2000, 85: 443-50.

18. Kesingland, A.C., Gentry, C.T., Panesar, M.S., Bowes, M.A., Vernier, J.-M., Cube, R., Walker, K., Urban, L. *Analgesic profile of the nicotinic acetylcholine receptor agonists, (+) epibatidine and ABT-594 in models of persistent inflammatory and neuropathic pain.* Pain 2000, 86: 113-8.

19. Bannon, A.W., Decker, M.W., Curzon, P. et al. *ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine]: A novel, orally effective antinociceptive agent acting via neuronal nicotinic acetylcholine receptors: II. In vivo characterization.* J Pharmacol Exp Ther 1998, 285: 787-94.

20. Bannon, A.W., Decker, M.W., Kim, D.J.B., Campbell, J.E., Arneric, S.P. *ABT-594, a novel cholinergic channel modulator, is efficacious in nerve ligation and diabetic neuropathy models of neuropathic pain.* Brain Res 1998, 801: 158-63.

21. Bitner, R.S., Nikkel, A.L., Curzon, P., Arneric, S.P., Bannon, A.W., Decker, M.W. *Role of the nucleus raphe magnus in antinociception produced by ABT-594: Immediate early gene responses possibly linked to neuronal nicotinic acetylcholine receptors on serotonergic neurons.* J Neurosci 1998, 18: 5426-32.

22. Jacobson, P.B., Komater, V., Wilcox, D.M., Namovic, M.T., Harris, R.R., Decker, M.W., Holladay, M.W., Arneric, S.P. *Anti-inflammatory activity of ABT-594 [(R)-5-(2-azetidinylmethoxy)-2-chloropyridine]: A novel, non-opioid nicotinic acetylcholine receptor agonist.* FASEB J 1998, 12(5): Abst 4412.

23. Belluardo, N., Mudò, G., Caniglia, G., Cheng, Q., Blum, M., Fuxe, K. *The nicotinic acetylcholine receptor agonist ABT-594 increases FGF-2 expression in various rat brain regions.* NeuroReport 1999, 10: 3909-13.

24. Meyer, M.D., Anderson, D.J., Campbell, J.E., Carroll, S., Marsh, K.C., Rodrigues, A.D., Decker, M.W. *Preclinical pharmacology of ABT-594: A nicotinic acetylcholine receptor agonist for the treatment of pain.* CNS Drug Rev 2000, 6: 183-94.

25. MacPherson, R.D. *The pharmacological basis of contemporary pain management.* Pharmacol Ther 2000, 88: 163-85.

26. Abbott Laboratories Global Pharmaceutical Pipeline May 9, 2001.

Additional References

Holladay, M.W., Wasicak, J.T., Lin, N.-H. et al. *Identification, initial pharmacological evaluation, and structure-activity relationships of ABT-594 as a potent, orally active analgesic agent acting via neuronal nicotinic acetylcholine receptors.* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.6.

Arneric, S.P., Anderson, D.J., Campbell, J.E., Kuntzweiller, T., Wasicak, J., Holladay, M.W., Pauly, J., Williams, M., Donnelly-Roberts, D. *In vitro pharmacology of ABT-594: A novel, non-opioid analgesic, neuronal nicotinic acetylcholine receptor (nAChR) ligand.* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.7.

Kesingland, A., Gentry, C., Bowes, M., Panesar, M., McKelvy, J., Vernier, J.-M., Urban, L., Walker, K. *Antinociceptive effects of nicotinic receptor agonists, (+)-epibatidine and ABT-594, in rat models of acute and chronic pain.* 9th World Congr Pain (Aug 22-27, Vienna) 1999, 25.

Bannon, A.W., Decker, M.W., Curzon, P., Buckley, M.J., Kim, D.J.B., Lynch, J.K., Wasicak, J.T., Arnold, W.H., Holladay, M.W., Arneric, S.P. *Characterization of ABT-594 in rats: A novel, orally effective antinociceptive agent acting via nicotinic acetylcholine receptors.* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.9.

Decker, M.W., Bannon, A.W., Buckley, M.J., Kim, D.J.B., Holladay, M.W., Ryther, K.B., Lin, N.-H., Wasicak, J.T., Williams, M., Arneric, S.P. *Antinociceptive effects of the novel cholinergic channel modulator, ABT-594, in mice.* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.8.

Donnelly-Roberts, D., Puttfarcken, P., Jacobs, I.X., Kuntzweiller, T., Arneric, S.P. *ABT-594: Neuroprotective effects in spinal cord (SC) cultures by a broad spectrum analgesic acting via nicotinic acetylcholine receptors (nAChRs).* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.12.

Puttfarcken, P.S., Manelli, A.M., Donnelly-Roberts, D., Arneric, S.P. *ABT-594 and (±)-epibatidine inhibit capsaicin-evoked substance P (SP) and calcitonin gene related peptide (CGRP) release from rat spinal cord slices via neuronal nicotinic acetylcholine receptors (nAChRs).* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.11.

Bitner, R.S., Nikkel, A.L., Bannon, A.W., Arneric, S.P., Decker, M.W. *Supraspinal c-fos induction produced by a novel cholinergic channel modulator analgesic ABT-594.* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.14.

Kim, D.J.B., Bannon, A.W., Campbell, J.E., Lynch, J.K., Bai, H., Holladay, M.W., Arneric, S.P., Decker, M.W. *Efficacy of ABT-594, a novel anti-nociceptive agent acting via nicotinic acetylcholine receptors, in a model of neuropathic pain.* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.10.

Curzon, P., Bitner, R.S., Nikkel, A.L., Bannon, A.W., Arneric, S.P., Decker, M.W. *Central mechanism involved in ABT-594 antinociception.* Soc Neurosci Abst 1997, 23(Part 2): Abst 477.13.

Anderson, D.J., Campbell, J.E., Lee, E., Holladay, M.W., Surber, B., Thomas, S., Arneric, S.P., Kuntzweiler, T.A. *[^{3}H]ABT-594 is a high-affinity selective neuronal nicotinic acetylcholine receptor (nAChR) radioligand.* Soc Neurosci Abst 1998, 24(Part 1): Abst 39.6.

Decker, M.W., Curzon, P., Holladay, M.W. *The role of neuronal nicotinic acetylcholine receptors in antinociception: Effects of ABT-594.* J Physiol - Paris 1998, 92: 221-4.

Holladay, M.W., Decker, M.W. *Discovery of ABT-594 and related neuronal nicotinic acetylcholine receptor modulators as analgesic agents: Medicinal chemistry and biology.* Adv Med Chem 2000, 5: 85-113.

Decker, M.W., Meyer, M.D. *Therapeutic potential of neuronal nicotinic acetylcholine receptor agonists as novel analgesics.* Biochem Pharmacol 1999, 58: 917-23.

Meyer, M.D., Decker, M.W., Rueter, L.E., Anderson, D.J., Dart, M.J., Kim, K.H., Sullivan, J.P., Williams, M. *The identification of novel structural compound classes exhibiting high affinity for neuronal nicotinic acetylcholine receptors and analgesic efficacy in preclinical models of pain.* Eur J Pharmacol 2000, 393: 171-7.

Flores, C.M. *The promise of pitfalls of a nicotinic cholinergic approach to pain management.* Pain 2000, 88: 1-6.