Drugs of the Future 2003, 28(3): 237-242

CCC: 0377-8282/2003

Nalfurafine Hydrochloride

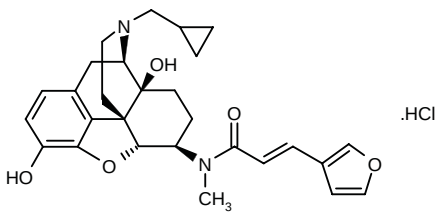
Prop INNM

Antipruritic
Analgesic
Kappa Opioid Agonist

TRK-820

N-[17-(Cyclopropylmethyl)-4,5(*R*)-epoxy-3,14-dihydroxymorphinan-6(*R*)-yl]-3-(3-furyl)-*N*-methyl-2(*E*)-propenamide hydrochloride

[4*R*-(4α,4aβ,7β,7aβ,12b*S*)]-*N*-[3-(Cyclopropylmethyl)-4a,9-dihydroxy-4,12-methano-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7-yl]-3-(3-furyl)-*N*-methyl-2(*E*)-propenamide hydrochloride



$C_{28}H_{32}N_2O_5$.HCl
Mol wt: 513.0307
CAS: 152658-17-8
CAS: 152657-84-6 (as free base)
EN: 217944

Abstract

Pruritus is a common symptom seen in 25-90% of uremic patients, especially those with chronic renal failure requiring hemodialysis. The cause and mechanism of induction of pruritus are not known. However, studies comparing hemodialysis patients with healthy subjects provided evidence that an imbalance in the endogenous opioid system may be responsible for pruritus with particular involvement of the kappa opioid system. Although existing kappa opioid receptor agonists lack morphine-like adverse effects, they are associated with dysphoria and psychotomimetic alterations. Thus, research efforts continue to focus on new kappa opioid agonists with novel structures to circumvent unwanted adverse effects. Nalfurafine hydrochloride is a novel kappa opioid receptor agonist that emerged using procedures incorporating a modification of the message-address concept. Nalfurafine was shown to be highly selective for the kappa opioid receptor *in vitro* and has displayed potent antipruritic activity *in vivo*. Moreover, a single dose of an oral formulation was shown to alleviate itch in hemodialysis patients suffering from severe pruritus. Nalfurafine has also shown potent antinociceptive activity both *in vitro* and *in vivo* in various animal models of pain and was also selected for further development as an analgesic for moderate and severe pain.

Synthesis

The reductocondensation of naltrexone (I) with *N*-methylbenzylamine (II) by means of sodium cyanoborohydride in THF gives the *N*-benzyl-*N*-methylaminomorphinan derivative (III), which is debenzylated by hydrogenation with H_2 over Pd/C in methanol to yield the methylaminomorphinan (IV). Finally, this compound is acylated with 3(*E*)-(3-furyl)acryloyl chloride and NaOH, Na_2CO_3 or triethylamine in methanol, THF or chloroform. Alternatively, methylaminomorphinan (IV) can be obtained by direct reductocondensation of naltrexone (I) with methylamine by means of H_2 over PtO_2 in methanol (1-4). Scheme 1.

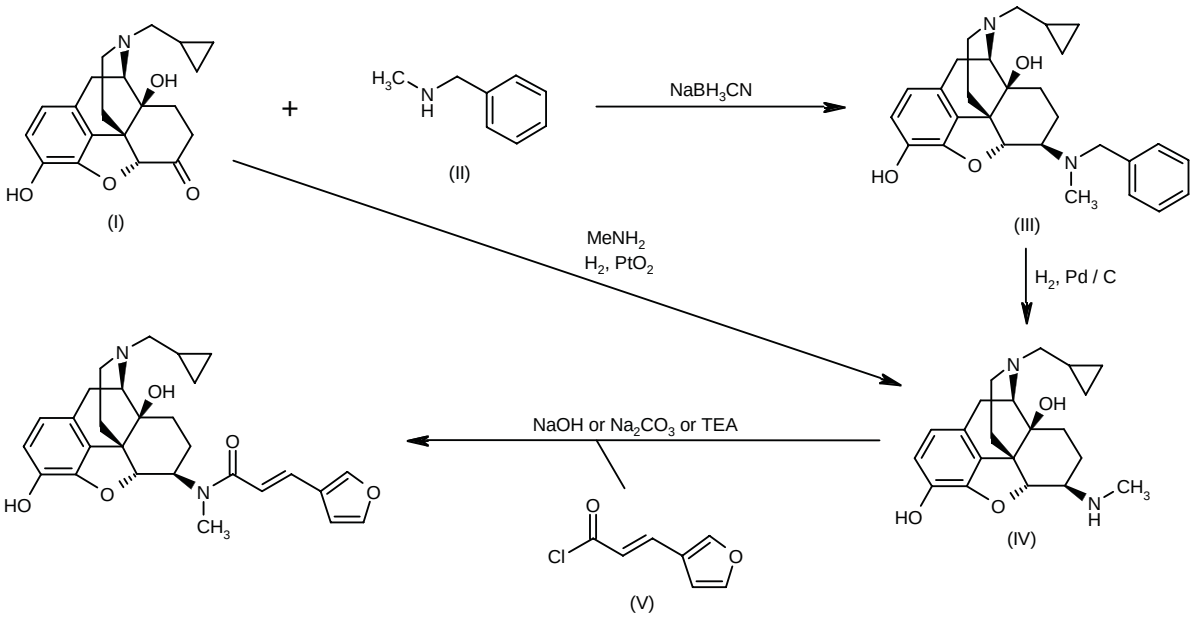
Introduction

Pruritus, a poorly localized sensation that elicits the desire to scratch, is a common distressing symptom of uremic patients that, although not life-threatening, can severely affect the quality of life. Many metabolic disorders are associated with uremia and are thought to be involved in the pathogenesis of pruritus. Chronic renal failure is among the systemic disorders which cause pruritus and its incidence ranges from 25-90% in these uremic patients; 37-90% of hemodialysis patients, 25-76% of peritoneal dialysis patients and 25-60% of chronic renal failure patients not on dialysis suffer from pruritus (5-7).

The mechanism and precise cause of pruritus are unknown. Skin biopsies from pruritic patients were shown to have high levels of calcium, magnesium and phosphorous so that phosphate binders and vitamin D supplemention, in addition to improved efficiency of dialysis (*e.g.*, increasing Kt/V), may improve but probably not eliminate pruritus (8-13). Histamine and serotonin have been implicated as possible mediators of uremic pruritus. Plasma histamine levels of some pruritic patients have

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

Scheme 1: Synthesis of Nalfurafine



been shown to be elevated although treatment with H_1 antihistamines results in relief in only some patients. Similarly, serotonin has also been suggested to play a role in cholestatic and uremic pruritus. However, administration of 5-HT_3 receptor blockers to patients with uremic pruritus was only effective in a few patients (6, 14-16). Therefore, uremic pruritus continues to be an important therapeutic challenge.

Studies have suggested that endogenous opioids may be involved in pruritus. Opioid receptors are classified into 3 types, mu, delta and kappa, according to their pharmacological profiles obtained in chronic spinal dogs, isolated tissues and radioligand bindings in brain membrane preparations. Following binding of endogenous ligands (*i.e.*, endorphins), opioid receptors regulate nociception, mood and responses to stress (17-21). Evidence suggesting that opioids may be involved in pruritus include the observation that morphine, a mu opioid receptor agonist, induces itching while naltrexone and naloxone, mu opioid receptor antagonists, suppress itching (22-27). Moreover, comparison of hemodialysis patients with uremic pruritus with age-matched healthy volunteers with uremic pruritus revealed that the serum ratio of β-endorphin (a mu opioid receptor agonist) and dynorphin A (a kappa opioid receptor agonist) increased proportionally with itch intensity in patients. Moreover, expression of the kappa opioid receptor was weaker than mu opioid receptor expression in patients as compared to heathy subjects. These results suggest that an imbalance in the endogenous opioid system may be responsible for pruritus with particular involvement of the kappa opioid system (28).

While clinically important mu opioid receptor agonists (*e.g.*, morphine and fentanyl) used in the treatment of pain are associated with several adverse effects including respiratory depression, constipation, dependence liability and pruritus of the face, neck and thorax, kappa opioid receptor agonists (*e.g.*, U-50488H, U-69593, PD-117302, CI-977) have potent antinociceptive effects without the morphine-like adverse effects. Unfortunately, these agents are also associated with the unwanted adverse effects of dysphoria and psychotomimetic alterations (29-35). In an attempt to discover effective agents for the treatment of uremic pruritus, researchers have therefore focused on the discovery of new kappa opioid agonists with novel structures in order to circumvent the unwanted adverse effects associated with these agents.

In an effort to design novel kappa opioid receptor agonists, a modified message-address concept was applied. The message-address concept was used to design the kappa opioid receptor antagonists. This concept is based on the idea that the 4,5-epoxymorphinan skeleton with a tyrosine-glycine moiety is the message subsite of the molecule required for opioid effects while the address subsite is responsible for opioid receptor selectively. When an agonist binds to a receptor, the receptor changes its structure leading to transduction of the agonist effect. In contrast, antagonists contain an accessory site which interferes with ligand-induced structure changes thus blocking any signal transduction and subsequent effects (36-38). Thus, using the message-address concept together with the removal of the accessory site of the molecule, novel kappa opioid receptor agonists were synthesized.

Nalfurafine hydrochloride (TRK-820) was synthesized as a novel selective kappa opioid receptor agonist by removing the accessory site of norbinaltorphimine and maintaining the 4,5-epoxymorphinan structure. Nalfurafine was shown to be highly selective for the kappa opioid receptor and has displayed potent kappa opioid receptor agonist activity *in vitro*. Nalfurafine exhibited potent antipruritic effects in animal models of pruritus and was chosen for further development as a treatment for uremic pruritus in patients receiving dialysis as a first indication. Moreover, nalfurafine exerted potent antinociceptive activity in animal models of pain *in vivo*, without inducing psychotomimetic activity. As a consequence, nalfurafine was also chosen for further development as an analgesic for moderate and severe pain (4).

Pharmacological Actions

The agonist activity and receptor selectivity of nalfurafine were examined *in vitro* using electrically stimulated guinea pig ileal longitudinal muscle and mouse vas deferens and receptor-selective antagonists (naloxone for the mu site, naltrindole for the delta site and norbinaltorphimine for the kappa site). Nalfurafine was 4000-fold more potent than morphine in both tissue preparations (IC_{50} = 0.0048 nM in ileum and 0.036 nM in mouse vas deferens) and was highly selective for the kappa site (mu/kappa = 279 for ileum and 104 for vas deferens; delta/kappa = 135 for mouse vas deferens) (4).

The agonist activity of nalfurafine was further examined *in vitro* using membrane preparations of CHO cells stably expressing cloned rat wild-type mu, delta and kappa opioid receptors and the nociceptin receptor. In competition (*i.e.*, [^{3}H]-bremazocine) binding assays, the agent displayed high affinity for the kappa opioid receptor (K_i = 3.5 ± 0.9 *vs.* 53 ± 12 nM and 1200 ± 300 for the mu and delta opioid receptors, respectively). Nalfurafine also had high affinity for the human kappa opioid receptor in membrane preparations from CHO cells (K_i = 0.11 nM). Experiments using CHO cells expressing cloned rat mutant kappa opioid receptors (E297K, E297W, E297A) showed that the high affinity of nalfurafine for the kappa opioid receptor required Glu^{297}. In saturation binding assays using [^{3}H]-nociceptin, nalfurafine bound with relatively low affinity (K_i = 380 ± 50 nM) which was 100 times lower than nociceptin. Further characterization of the pharmacological activity of nalfurafine on various opioid and nociceptin receptor types showed that nalfurafine concentration-dependently inhibited forskolin-stimulated cAMP accumulation in CHO cells expressing the rat kappa opioid receptor (IC_{50} = 0.15 ± 0.08 nM; I_{max} = 81 ± 3%). The agent also inhibited forskolin-stimulated cAMP accumulation in CHO cells expressing the mu opioid receptor although effects were less marked (IC_{50} = 8.3 ± 1.4 nM ; I_{max} = 69 ± 3%). Nalfurafine displayed very weak activity in inhibiting forskolin-stimulated cAMP accumulation in CHO cells expressing the delta opioid receptor (IC_{50} = > 1000 nM) and had no inhibitory activity in CHO cells expressing the nociceptin receptor. In addition, nalfurafine (100 μM) significantly antagonized (88 ± 6%) nociceptin-mediated inhibition of cAMP accumulation in these cells. Together these results indicate that nalfurafine acts as a full agonist for the kappa opioid receptor, a partial agonist for the mu opioid receptor and a low-affinity antagonist of the nociceptin receptor (39, 40).

Nalfurafine was shown to antagonize mu opioid receptors in an *in vitro* study examining DAMGO (a selective mu opioid receptor agonist)-induced G-protein activation (*i.e.*, [^{35}S]-GTPγS binding in mouse pons/medulla membrane preparations). Treatment with nalfurafine alone resulted in small but significant increases (11.8 ± 3.2 *vs.* 97.7 ± 2.4% for DAMGO) in GTPγS binding; this effect was completely blocked by norbinaltorphimine. However, nalfurafine (0.1-10 μM) concentration-dependently and significantly attenuated DAMGO (10 μM)-induced increases in GTPγS binding indicating antagonism of the mu opioid receptor (41).

Nalfurafine demonstrated potent antipruritic activity *in vivo* in a mouse pruritogen-induced scratching model. Nalfurafine (p.o. 30 min before injection of the pruritogen) dose-dependently inhibited scratching behavior induced by substance P (ED_{50} = 19.6 μg/kg; significant effects observed with 100 μg/kg) or histamine (ED_{50} = 7.3 μg/kg significant effects observed with 30 and 100 μg/kg). At the doses tested, the agent had no suppressive effects on spontaneous locomotor activity indicating that inhibition of scratching was not due to alterations of general behavior. Norbinaltorphimine dose-dependently antagonized nalfurafine-inhibited scratching suggesting that the antipruritic activity of the agent was via the kappa opioid receptor (42).

Nalfurafine may be effective against severe, antihistamine-resistant pruritus. The agent effectively and dose-dependently reduced morphine (0.3 nmol intracisternal)-induced scratching behavior in mice with no obvious alteration in behavior seen. Ketotifen had little effect in this model (43).

The efficacy of nalfurafine (0.125, 0.25 and 0.5 μg/kg i.v. or 1, 2 and 4 μg/kg i.g.) in inhibiting morphine (1 mg/kg i.v. 15 or 30 min before i.v. and i.g. nalfurafine, respectively)-induced scratching was demonstrated *in vivo* in rhesus monkeys. While nalfurafine doses of 0.25 and 0.5 μg/kg i.v. reduced systemic skin scratching to 16.9-35.7% of the control levels, 0.125 μg/kg i.v. decreased scratching by about 65%. Nalfurafine was also effective when administered via the i.g. route. Nalfurafine doses of 4 μg/kg i.g. reduced skin scratching to 23.4% and doses of 1 and 2 μg/kg did so to 71.8-84.2% of the control level, respectively. Nalfurafine did not induce scratching activity when administered alone (44).

In addition, to potent antipruritic effects, nalfurafine was also shown to have marked antinociceptive effects in several *in vivo* animal models of pain (4, 46-52).

ED_{50} values for nalfurafine obtained in the acetic acid writhing and tail flick tests in mice were 0.0033 and 0.62 mg/kg s.c., respectively. Nalfurafine was 85-140 times more potent than morphine and its antinociceptive effects were antagonized by norbinaltorphimine (4).

Nalfurafine showed antinociceptive efficacy in the paw pressure, formalin and thermal injury tests in rats. ED_{50} values for the agent after s.c. and i.m. administration in the paw pressure test were 0.064 and 0.075 mg/kg, respectively, which were 20 times more potent than morphine (ED_{50} = 1.3 and 1.6 mg/kg, respectively) and 70-fold more potent than pentazocine (ED_{50} = 5 and 3.2 mg/kg, respectively). Nalfurafine dose-dependently (0.0025-0.02 mg/kg s.c. 15 min before formalin) and markedly inhibited the second phase of the formalin nociceptive response (ED_{50} = 0.0096 *vs.* 0.975 mg/kg s.c. for morphine); the agent only slightly inhibited the first phase of the formalin nociceptive response. Treatment of rats subjected to thermal injury to the hind foot with nalfurafine (0.1, 0.2 and 0.4 μg in 20 μl saline injected at the site of injury) resulted in dose-dependent peripheral analgesic activity (45, 46).

Nalfurafine (0.01 and 0.03 mg/kg i.m.) was also effective in inducing antinociceptive effects in the hot water tail withdrawal test in cynomolgus monkeys. The agent was 295- and 495-fold more potent than morphine when temperatures of 50 and 55 °C were used, respectively. The antinociceptive effects of nalfurafine were sustained for more than 6 h postdosing (47).

The efficacy of nalfurafine in suppressing neuropathic pain was demonstrated in a murine human zosteriform-like pain model (*i.e.*, primary sensory neurons infected with herpes simplex virus type 1) and in a modified Seltzer model (*i.e.*, partial sciatic nerve ligation). Both nalfurafine and morphine dose-dependently inhibited allodynia and hyperalgesia without affecting spontaneous motor activity; norbinaltorphimine but not naltrexone antagonized the effects of nalfurafine. Repeated dosing (b.i.d. x 4) diminished the effects of morphine in the human zosteriform-like pain model but not those of nalfurafine (48).

Nalfurafine could be effective in reducing the unwanted side effects associated with morphine and may be an option for the treatment of cocaine addiction. Nalfurafine (0.01 and 0.03 mg/kg mg/kg s.c.) significantly suppressed the rewarding and locomotor-enhancing effects of morphine and development of physical dependence in mice and attenuated the discriminative stimulus and rewarding effects of cocaine in rats (49-51).

Clinical Studies

The antipruritic efficacy of single-dose nalfurafine (10 μg p.o. at 7:00 AM) was demonstrated in a trial involving 8 patients on maintenance hemodialysis suffering from severe pruritus who did not respond to antihistamine therapy. Mean 100 mm visual analogue scale (VAS) scores were significantly reduced with nalfurafine treatment (12.2 and 1.8 mm at 4 and 12 h postdosing *vs.* 54.2 mm at baseline). A significant improvement was also noted in itch intensity according to a 5 grade categorization. The antipruritic effects of the agent were found to be almost proportional to plasma nalfurafine concentrations. Adverse events associated with treatment were mild drowsiness and weakness. Larger clinical studies have been initiated to further examine the efficacy and safety of nalfurafine as a treatment for severe pruritus (53).

An injectable formulation of nalfurafine is currently being developed for the treatment of uremic pruritus in patients receiving dialysis as a first indication. A marketing application was filed at the end of 2002 in Sweden. Nalfurafine is expected to be marketed in Europe in 2004 as a treatment for uremic pruritus. In addition, the compound continues to undergo development as treatment for moderate and severe pain (54).

Source

Toray Industries Inc. (JP); licensed to Daiichi Pharmaceutical Co., Ltd. (JP) for codevelopment in Japan and to Fujisawa Pharmaceutical Co., Ltd. (JP) for Europe.

References

1. Nagase, H., Kawai, K., Kawamura, K., Hayakawa, J., Endo, T. (Toray Industries, Inc.). *Morphinan deriv. and medicinal use.* EP 0577847, EP 0846693, JP 1994509616, US 6277859, US 6323212, WO 9315081.

2. Nagase, H., Hayakawa, J., Kawamura, K., Kawai, K., Endoh, T. (Toray Industries, Inc.). *Morphinan deriv. and medicinal use.* EP 0663401, JP 1995505061, US 6177438, WO 9503308.

3. Nagase, H., Kawai, K., Endo, T., Ueno, S., Negishi, Y. (Toray Industries, Inc.). *Antitussive.* EP 0657163, JP 1995503397, US 5739145, WO 9501178.

4. Nagase, H., Hayakawa, J., Kawamura, K., Kawai, K., Takezawa, Y., Matsuura, H., Tajima, C., Endo, T. *Discovery of a structurally novel opioid kappa agonist derived from 4,5-epoxymorphinan.* Chem Pharm Bull 1998, 46: 366-9.

5. Schwartz, I.F., Iaina, A. *Management of uremic pruritus.* Semin Dial 2000, 13: 177-80.

6. Balaskas, E.V., Bamihas, G.I., Karamouzis, M., Voyiatzis, G., Tourkantonis, A. *Histamine and serotonin in uremic pruritus: Effect of ondansetron in CAPD-pruritic patients.* Nephron 1998, 78: 395-402.

7. Balaskas, E.V., Oreopoulos, D.G. *Uremic pruritus (Part I).* Dial Transplant 1992, 21: 192-205.

8. Masi, C.M., Cohen, E.P. *Dialysis efficacy and itching in renal failure.* Nephron 1992, 62: 257-61.

9. Hiroshige, K., Kabashima, N., Takasugi, M., Kuroiwa, A. *Optimal dialysis improves uremic pruritus.* Am J Kidney Dis 1995, 25: 413-9.

10. Mettang, T., Fritz, P., Weber, J., Machleidt, C., Hubel, E., Kohlmann, U. *Uremic pruritus in patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). The role of plama histamine and skin mast cells.* Clin Nephrol 1990, 34: 136-41.

11. Stahle-Backdahl, M. *Uremic pruritus: Clinical and experimental studies.* Acta Dermato-Venereol 1989, 145(Suppl.): 1-38.

12. Stockenhuber, F., Kurz, R.W., Sertl, K., Grimm, G., Balcke, P. *Increased plasma histamine levels in uremic pruritus.* Clin Sci 1990, 79: 477-82.

13. Gill, D.S., Fonseca, V.A., Barradas, M.A., Balliod, R., Moorhead, J.F., Dandona, P. *Plasma histamine in patients with chronic renal failure and nephrotic syndrome.* J Clin Pathol 1991, 44: 243-5.

14. Raja, R.M. *Uremic pruritus.* Semin Dial 1993, 6: 350-2.

15. Balaskas, E.V., Oreopoulos, D.G. *Uremic pruritus (Part II).* Dial Transplant 1992, 21: 282-4.

16. Johnson, C.A. *An update on uremic pruritus.* MedFacts 2002, 4(1).

17. Prous Science Drug R&D Backgrounders: *Pain (online publication).* Updated March 19, 2003.

18. Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., Gilbert, P.E. *The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog.* J Pharmacol Exp Ther 1976, 197: 517-32.

19. Lord, J.A., Waterfield, A.A., Hughes, J., Kosterlitz, H.W. *Endogenous opioid peptides: Multiple agonists and receptors.* Nature 1977, 267: 495-9.

20. Schulz, R., Faase, E., Wuster, M., Herz, A. *Selective receptors for β-endorphin on the rat vas deferens.* Life Sci 1979, 24: 843-9.

21. Kosterlitz, H.W., Paterson, S.J., Robson, L.E. *Characterization of the kappa subtype of the opiate receptor in the guinea-pig brain.* Br J Pharmacol 1981, 73: 939-49.

22. Cousins, M.J., Mather, L.E. *Intrathecal and epidural administration of opioids.* Anesthesiology 1984, 61: 276-310.

23. Ballantyne, J.C., Loach, A.B., Carr, D.B. *Itching after epidural and spinal opiates.* Pain 1988, 33: 149-60.

24. Bernstein, J.E., Swift, R.M., Soltani, K., Lorincz, A.L. *Antipruritic effect of an opiate antagonist, naloxone hydrochloride.* J Invest Dermatol 1982, 78: 82-3.

25. Bergasa, N.V., Talbot, T.L., Alling, D.W. *A controlled trial of naloxone infusions for the pruritus of chronic cholestasis.* Gastroenterology 1992, 102: 544-9.

26. Peer, G., Kivity, S., Agami, O., Fireman, E., Silverberg, D., Blum, M., Laina, A. *Randomised crossover trial of naltrexone in uraemic pruritus.* Lancet 1996, 348: 1552-4.

27. Metz, D., Reimann, S., Beissert, S., Luger, T. *Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases.* J Am Acad Dermatol 1999, 41: 533-9.

28. Kumagai, H., Sasamura, H., Hayashi, M., Saruta, T. *Imbalance between endogenous mu and kappa opioid systems as a pathogenesis of itching of patients on maintenance hemodialysis.* ASN/ISN World Congr Nephrol (Oct 13-17, San Francisco) 2001, 391A.

29. Popio, K.A., Jackson, D.H., Ross, A.M., Schreiner, B.F., Yu, P.N. *Hemodynamic and respiratory effects of morphine and butorphanol.* Clin Pharmacol Ther 1978, 23: 281-7.

30. Stewart, J.J., Weisbrodt, N.W., Burks, T.F. *Central and peripheral actions of morphine on intestinal transit.* J Pharmacol Exp Ther 1978, 205: 547-55.

31. Martin, W.R., Soloan, J.W. In: Drug Addiction 1. Handbook of Experimental Pharmacology, W.R. Martin (Ed.), Springer-Verlag, Heidelberg, 1977, 43-158.

32. Lahti, R.A., Von Voigtlander, P.F., Barsuhn, C. *Properties of a selective kappa agonist, U-50,488H.* Life Sci 1982, 31: 2257-60.

33. Lahti, R.A., Mickelson, M.M., McCall, J.M., Von Voigtlander, P.F. *[^{3}H]U-69593 a highly selective ligand for the opioid kappa receptor.* Eur J Pharmacol 1985, 109: 281-4.

34. Clark, C.R., Birchmore, B., Sharif, N.A., Hunter, J.C., Hill, R.G., Hughes, J. *PD117302: A selective agonist for the kappa opioid receptor.* Br J Pharmacol 1988, 93: 618-26.

35. Hunter, J.C., Leighton, G.E., Meecham, K.G., Boyle, S.J., Horwell, D.C., Rees, D.C., Hughes, J. *CI-977, a novel and selective agonist for the kappa opioid receptor.* Br J Pharmacol 1990, 101: 183-9.

36. Portoghese, A.S., Lipkowski, A.W., Takemori, A.E. *Bimorphinans as highly selective, potent kappa opioid receptor antagonists.* J Med Chem 1987, 30: 238-9.

37. Portoghese, P.S., Sultana, M., Nagase, H., Takemori, A.E. *Application of the message-address concept in the design of highly potent and selective non-peptide delta opioid receptor antagonists.* J Med Chem 1988, 31: 281-2.

38. Nogrady, T. In: Medicinal Chemistry, a Biochemical Approach, Oxford University Press, New York, 1985, 68-9.

39. Seki, T., Awamura, S., Kimura, C., Ide, S., Sakano, K., Minami, M., Nagase, H., Satoh, M. *Pharmacological properties of TRK-820 on cloned mu, delta and kappa opioid receptors and nociceptin receptor.* Eur J Pharmacol 1999, 376: 159-67.

40. Sekiyama, H., Tanaka, T., Kawamura, K., Collins, J.G., Nagase, H. *Pharmacological properties and peripheral analgesic effect of a kappa selective opioid TRK-820 and its quaternary derivative, TAN-684, which minimally crosses the blood-brain barrier.* Annu Meet Am Soc Anesthesiol (ASA) (Oct 14-18, San Francisco) 2000, Abst A-800.

41. Mizoguchi, H., Hung, K.C., Leitermann, R., Narita, M., Nagase, H., Suzuki, T., Tseng, L.F. *Blockade of mu opioid receptor-mediated G protein activation and antinociception by TRK-820 in mice.* Eur J Pharmacol 2003, 461: 35-9.

42. Togashi, Y., Umeuchi, H., Okano, K. et al. *Antipruritic activity of the kappa opioid receptor agonist, TRK-820.* Eur J Pharmacol 2002, 435: 259-64.

43. Umeuchi, H., Tanaka, T., Kawamura, K., Okano, K., Endoh, T., Kamei, J., Nagase, H. *Anti-pruritic effect of a kappa opioid receptor agonist TRK-820.* 76th Annu Meet Jpn Pharmacol Soc (March 24-26, Fukuoka) 2003, Abst 2P327.

44. Fuziwara, A., Wakasa, Y., Umeuchi, H., Tanaka, T., Endo, T., Nagase, H. *Inhibitory effects of TRK-820 on systemic skin scratching induced by intravenous morphine in rhesus monkeys.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-771.

45. Endoh, T., Tajima, A., Suzuki, T., Kamei, J., Narita, M., Tseng, L., Nagase, H. *Characterization of the antinociceptive effects of TRK-820 in the rat.* Eur J Pharmacol 2000, 387: 133-40.

46. Sekiyama, H., Shimada, S.G., Franco, K., Iwase, Y., Nagase, H., Utsumi, J., Collins, J.G. *Peripheral administration of a kappa selective agonist (TRK-820) blocks thermally induced hyperalgesia in rats.* 9th World Congr Pain (Aug 22-27, Vienna) 1999, Abst 119.

47. Endoh, T., Tajima, A., Izumimoto, N. et al. *TRK-820, a selective kappa opioid agonist, produces potent antinociception in cynomolgus monkeys.* Jpn J Pharmacol 2001, 85: 282-90.

48. Hirakata, M., Takasaki, I., Suzuki, T., Nakao, K., Okano, K., Tanaka, T., Kuraishi, Y., Nagase, H. *The effects of TRK-820, a kappa opioid agonist, on neuropathic pain.* Jpn J Pharmacol 2002, 88(Suppl. 1): Abst P-110.

49. Tsuji, M., Takeda, H., Matsumiya, T., Nagase, H., Yamazaki, M., Narita, M., Suzuki, T. *A novel κ-opioid receptor agonist, TRK-820, blocks the development of physical dependence on morphine in mice.* Life Sci 2000, 66: PL353-8.

50. Tsuji, M., Takeda, H., Matsumiya, T., Nagase, H., Narita, M., Suzuki, T. *The novel kappa opioid receptor agonist TRK-820 suppresses the rewarding and locomotor-enhancing effects of morphine in mice.* Life Sci 2001, 68: 1717-25.

51. Mori, T., Nomura, M., Nagase, H., Narita, M., Suzuki, T. *Effects of a newly synthesized kappa opioid receptor agonist, TRK-820, on the discriminative stimulus and rewarding effects of cocaine in rats.* Psychopharmacology 2002, 161: 17-22.

52. Endoh, T., Matsuura, H., Tajima, A. et al. *Potent antinociceptive effects of TRK-820, a novel kappa opioid receptor agonist.* Life Sci 1999, 65: 1685-94.

53. Kumagai, H., Utsumi, J., Matsukawa, S., Sasamura, H., Moritake, S., Ona, S., Nagase, H., Saruta, T. *Effects of a novel opioid kappa (kappa)-agonist, TRK-820, for treating itching of patients on maintenance hemodialysis.* ASN/ISN World Congr Nephrol (Oct 13-17, San Francisco) 2001, 391A.

54. *Toray and Fujisawa to codevelop TRK-820 in Europe.* DailyDrugNews.com (Daily Essentials) February 3, 2003.

Additional References

Tsuji, M., Yamazaki, M., Takeda, H., Matsumiya, T., Nagase, H., Tseng, L.F., Narita, M., Suzuki, T. *The novel κ-opioid receptor agonist TRK-820 has no affect on the development of antinociceptive tolerance to morphine in mice.* Eur J Pharmacol 2000, 394: 91-5.

Okano, K., Togashi, Y., Umeuchi, H., Ando, N., Tanaka, T., Kawamura, K., Endo, T., Kamei, J., Nagase, H. *Anti-pruritic effect of opioid kappa receptor agonist TRK-820.* 7th World Conf Clin Pharmacol Ther (July 15-20, Florence) 2000, Abst 1105.

Togashi, Y., Yoshizawa, Y., Honda, T., Umeuchi, H., Tanaka, T., Kawamura, K., Okano, K., Endo, T., Nagase, H. *Antipruritic effects of opioid kappa receptor agonist TRK-820.* Jpn J Pharmacol 2000, 82(Suppl. 1): Abst P-440.

Saitoh, A., Endoh, T., Izumoto, N., Suzuki, T., Ueno, S., Narita, M., Tseng, L.F., Nagase, H. *Pharmacological profiles of TRK-820, a novel κ-opioid receptor agonist.* Soc Neurosci Abst 1999, 25(Part 1): Abst 490.3.

DeHaven, R.N., Chang, A.C., Daubert, J.D., Cassel, J.A., Gottshall, S.L., DeHaven-Hudkins, D.L., Mansson, E., Yu, G. *TRK-820 exhibits both kappa agonist and mu antagonist properties.* Soc Neurosci Abst 1998, 24(Part 1): Abst 352.6.

Ozaki, S., Suzuki, T., Misawa, M., Nagase, H. *Studies on drug dependence (Rept. 320): Interaction between β-endorphin and endomorphin-1 or endomorphin-2 induced antinociception.* Jpn J Pharmacol 1999, 79(Suppl. I): Abst O-169.

Xiao, P., Kubo, H., Ohsawa, M., Higashiyama, K., Nagase, H., Yan, Y.-N., Li, J.-S., Kamei, J., Ohmiya, S. *The antinociceptive effects of matrine type lupin alkaloids.* 18th Symp Med Chem (Nov 25-27, Kyoto) 1998, Abst 1-P-22.

Nagase, H. *Rational design and synthesis of non-peptide kappa opioid agonist.* Jpn J Pharmacol 1997, 73(Suppl. 1): Abst S23-5.