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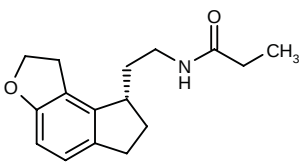
TAK-375

Treatment of Insomnia
Treatment of Circadian Rhythm Disorders
Melatonin MT_1/MT_2 Agonist

Ramelteon

(–)-(*S*)-*N*-[2-(2,6,7,8-Tetrahydro-1*H*-indeno[5,4-*b*]furan-8-yl)ethyl]propionamide



$C_{16}H_{21}NO_2$

Mol wt: 259.3469

CAS: 196597-26-9

EN: 255673

Abstract

Melatonin is a neurohormone produced in the pineal gland that is involved in the regulation of circadian rhythm function. It works through activation of its intrinsic receptors found in the suprachiasmatic nucleus (SCN) within the hypothalamus. Melatonin synthesis is under direct neural control from SCN firing. The sleep/wake cycle is a circadian rhythm controlled by this neural complex. Problems in the functioning of this system can therefore lead to sleep disorders. While melatonin itself has been shown to be effective in the treatment of sleep disorders, problems due to its ubiquitous action in the brain have limited its use for this indication. TAK-375 is a potent melatonin receptor agonist, specific for the ML_1 receptor subtype known to be intricately involved in circadian rhythm function. TAK-375 has been heralded as an exciting new drug candidate for the treatment of patients with insomnia and circadian rhythm dysfunction. Phase III trials are currently under way to test the drug's viability for use in patients with sleep disorders.

Synthesis

TAK-375 can be prepared by several related ways:

a) Reaction of 2,3-dihydrobenzofuran (I) with either dichloromethyl methyl ether by means of $TiCl_4$ in dichloromethane (1) or dimethylformamide and $POCl_3$ (2) gives 2,3-dihydrobenzofuran-5-carbaldehyde (II), which is condensed with the phosphonate (III) by means of either NaH in THF (1) or *t*-BuONa in toluene (2) to yield the propenoic ester (IV). Reduction of compound (IV) with H_2 over Pd/C in ethanol affords the saturated propionic ester (V), which is brominated with Br_2 and Fe in AcOH to provide the 6,7-dibromo derivative (VI). Hydrolysis of compound (VI) with NaOH in THF/water (1) or in acidic medium (2) yields the propionic acid derivative (VII), which by reaction with hot $SOCl_2$ affords the corresponding acyl chloride (VIII). Cyclization of compound (VIII) by means of $AlCl_3$ in dichloroethane provides 4,5-dibromo-2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-one (IX). The hydrogenolytic debromination of compound (IX) by means of H_2 over Pd/C in AcOH gives 2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]-furan-8-one (X), which is submitted to a Wittig condensation with the phosphonate (XI) by means of either NaH in THF (1) or NaOMe in toluene (2) to yield 2-(2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-ylidene)acetonitrile (XII). The selective reduction of the cyano group of (XII) by means of H_2 over Raney cobalt in either ethanol/NH_3 (1) or toluene/MeOH (2) affords 2-(2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-ylidene)ethylamine (XIII), which is condensed with propionyl chloride (XIV) by means of TEA in THF to provide the propionamide (XV). Finally, this compound is enantioselectively reduced with H_2 over a chiral Ru catalyst [$Ru(OAc)_2$-(*S*)-BINAP] in methanol (1). Scheme 1.

b) Alternatively, the reduction of 2-(2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-ylidene)acetonitrile (XII) with H_2 over Ra-Ni in ethanol/NH_3 gives 2-(2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-yl)ethylamine (XVI), which is acylated with propionyl chloride (XIV) and TEA in DMF to yield the racemic propionamide (XVII). Finally, this compound is submitted to optical resolution by means of chiral HPLC (1). Scheme 1.

c) Alternatively, asymmetric reduction of compound (XIII) with H_2 and a chiral Ru catalyst [$Ru(OAc)_2$-(*S*)-BINAP] in toluene/MeOH affords 2-[2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8(*S*)-yl]ethylamine (XVIII), which is finally acylated with propionyl chloride (XIV) and NaOH in aqueous THF (2). Scheme 1.

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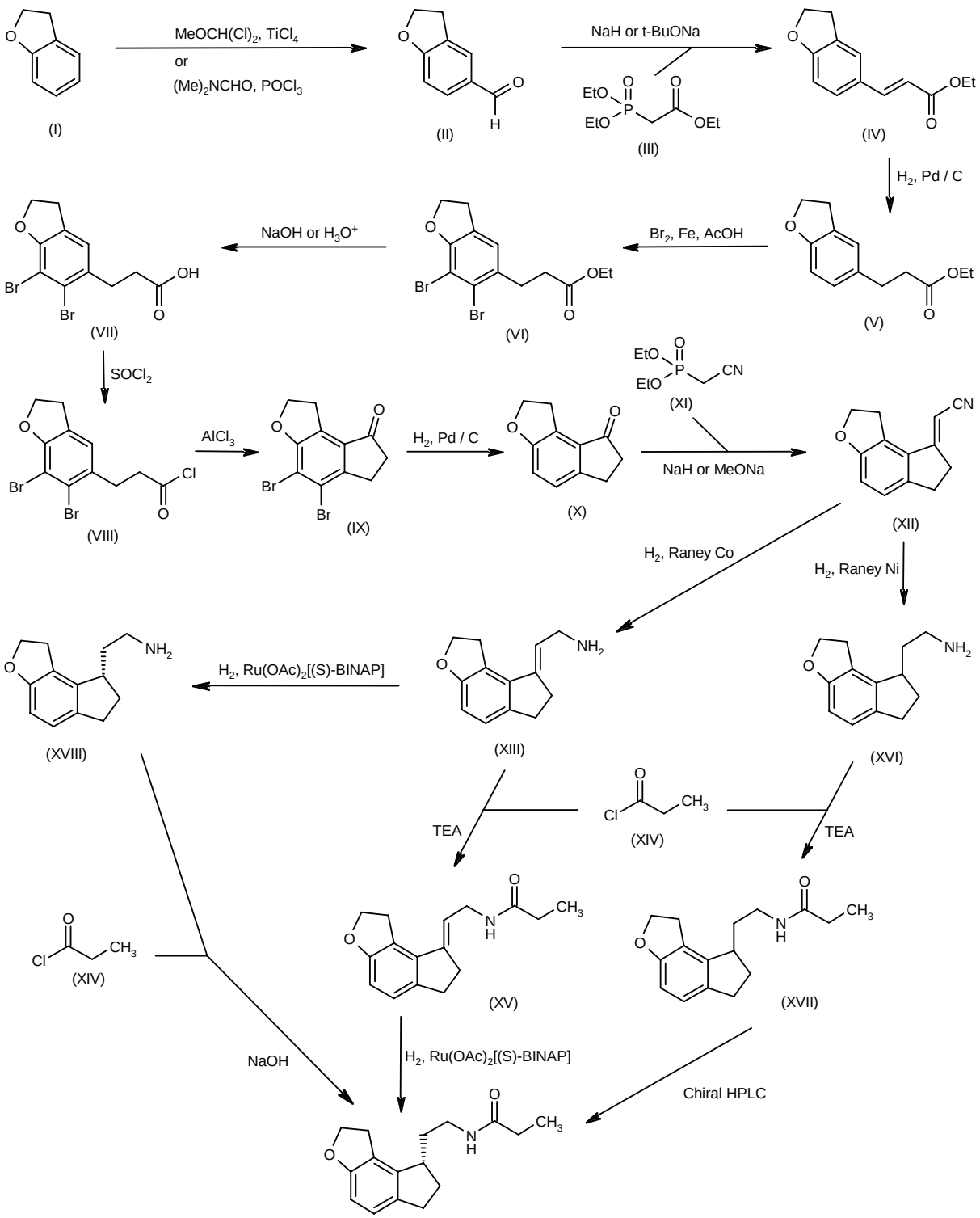
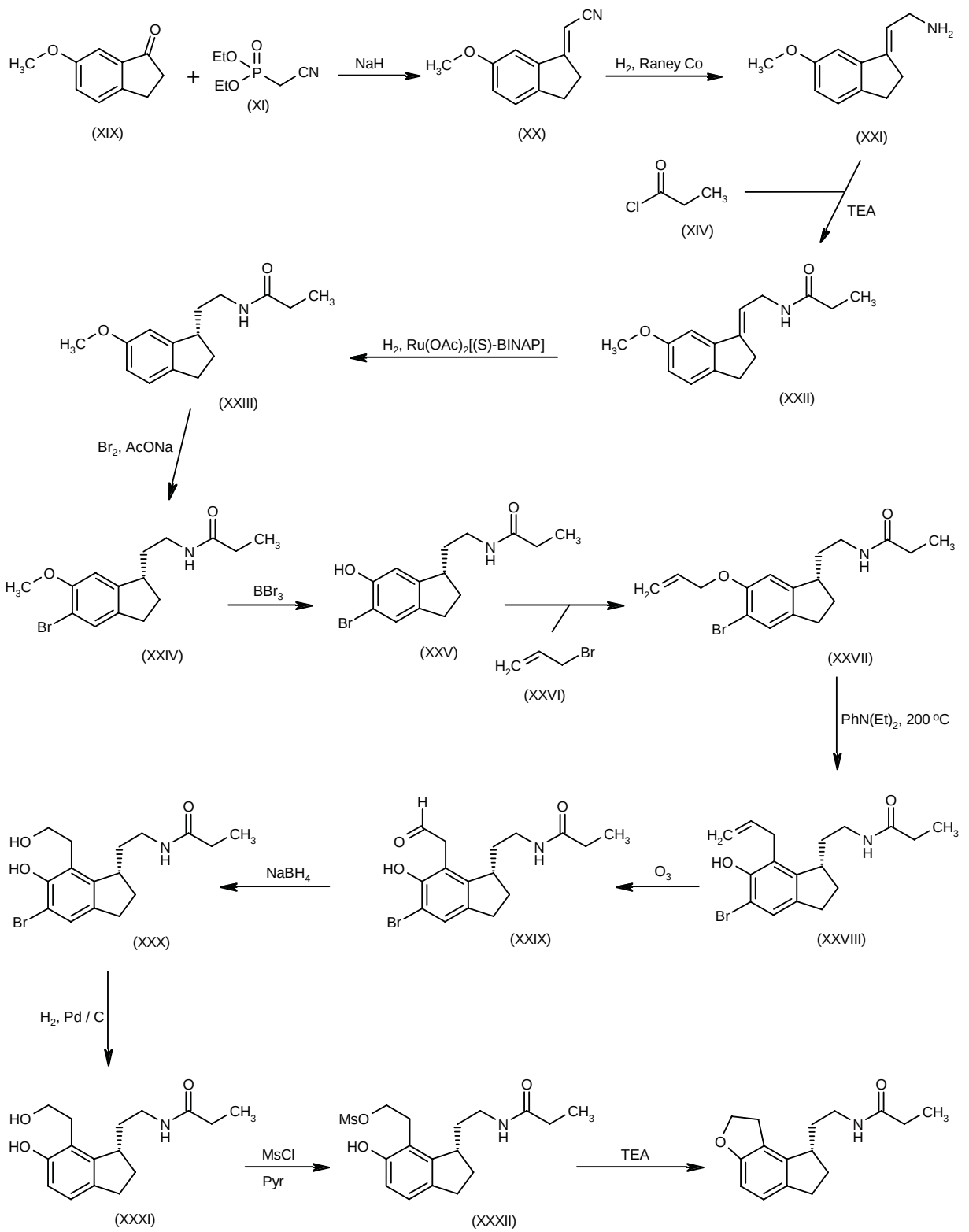
Scheme 1: Synthesis of TAK-375



Scheme 2: Synthesis of TAK-375



d) Condensation of 6-methoxyindan-1-one (XIX) with phosphonate (XI) by means of NaH in THF gives 2-(6-methoxyindan-1-ylidene)acetonitrile (XX), which is hydrogenated with H_2 over Raney cobalt in ethanol/NH_3 to yield 2-(6-methoxyindan-1-ylidene)ethylamine (XXI). Acylation of compound (XXI) with propionyl chloride (XIV) and TEA in THF affords the corresponding amide (XXII), which is submitted to an asymmetric reduction with H_2 and a chiral Ru catalyst [$Ru(OAc)_2$-(*S*)-BINAP] to provide *N*-[2-[6-methoxyindan-1(*S*)-yl]ethyl]propionamide (XXIII). Bromination of propionamide (XXIII) with Br_2 and NaOAc in methanol gives the 5-bromo derivative (XXIV), which is demethylated by means of BBr_3 in dichloromethane to yield the hydroxy compound (XXV). Reaction of alcohol (XXV) with allyl bromide (XXVI) by means of NaH in DMF affords the allyl ether (XXVII), which is submitted to a Claisen rearrangement in *N,N*-diethylaniline at 200 °C to provide the 7-allyl derivative (XXXVIII). Reaction of compound (XXVIII) with ozone in methanol gives the acetaldehyde derivative (XXIX), which is reduced with $NaBH_4$ in methanol to yield the ethanol derivative (XXX). The hydrogenolytic debromination of compound (XXX) by means of H_2 over Pd/C in methanol/TEA affords the dihydroxy compound (XXXI), which is treated with MsCl and pyridine to provide the mesylate (XXXII). Finally, this compound is cyclized by means of TEA in refluxing ethyl acetate (3). Scheme 2.

Introduction

The circadian rhythm of sleep is controlled by a series of neural pathways in the human brain. Melatonin is the neurohormone ultimately responsible for synchronization of circadian rhythms. Melatonin production, and consequently sleep onset, is controlled by a complex myriad of negative and positive feedback inputs from higher centers.

Sleep initiation begins with the recognition of the environmental light/dark cycle by receptors in the retina. This information is transferred to neurons in the hypothalamus via the retino-hypothalamic tract. The suprachiasmatic nucleus (SCN) found within the hypothalamus is the pacemaker for all circadian rhythm activity in the human brain. SCN neurons exhibit intrinsic circadian rhythmicity in response to entrainment from the light/dark cycle.

The circadian rhythmicity of SCN firing is subsequently conveyed to the pineal gland, the structure that controls the release of melatonin. The SCN sends impulses, via a series of neurons in the hypothalamus and spinal cord, up to the pineal gland to stimulate melatonin secretion. The amount of melatonin circulating in the blood has been shown to rise and fall during a day. Its production is analogous to normal human sleep patterns. It is the rhythmic release of the endogenous neurohormone melatonin that ultimately leads to sleep onset (4).

Disruption of circadian rhythm patterns has been implicated as an etiological factor in the pathophysiology of sleep disorders. The sleep/wake cycle length is characteristically just over 24 h in humans, and is therefore entrained to the 24-h clock each day by environmental cues. Disruption of this circadian rhythm anywhere along its neuronal pathway can potentially lead to sleep disorders. The normalization of such impairments has therefore been heralded as a potential new therapeutic target for the treatment of insomnia (5).

Melatonin has the ability to reset circadian rhythms normally regulated externally via the light/dark cycle. This ability to alter circadian rhythm synchronization implies its potential use in the treatment of conditions associated with problems in this area (6).

Exogenous melatonin administration is effective in treating sleep disorders and is unique in that it does not possess the sedative properties normally brought about by more traditional opiate-based or benzodiazepine preparations. However, it has been associated with a plethora of side effects due to its nonspecific binding at a number of sites throughout the brain. Problems also arise due to its short half-life (15-20 min) and reduced bioavailability. A number of melatonin analogues have been strategically designed to overcome the problems associated with melatonin administration (3, 7). One such compound, TAK-375 (ramelteon), was shown to be a potent and specific melatonin antagonist and was selected for further development.

Pharmacological Actions

TAK-375 binds specifically to melatonin receptor sites in the hypothalamus, thus enabling it to mimic the effects of melatonin on sleep induction and circadian rhythm regulation (2, 8, 9).

Cloning studies have identified two distinct groups of melatonin receptors in the SCN, namely ML_1 (MT_1/MT_2) annd ML_2 (MT_3) receptors. High-affinity ML_1 receptors are responsible for melatonin's effects on circadian rhythm function. Both ML_1 and ML_2 receptor subtypes belong to the family of G-protein-coupled receptors mediated by their inhibitory action on adenylate cyclase. The ML_1 receptor is located exclusively in the SCN, while the ML_2 receptor is also found in the neural retina as well as other areas throughout the body. Its effects have subsequently been shown to extend beyond the induction of sleep (10, 11).

The binding affinities of TAK-375 for these specific melatonin receptor subtypes were tested via binding assays using chick forebrain and hamster brain preparations. Chick forebrain tissue is known to be rich in ML_1 receptors, as is hamster brain tissue with ML_2 receptors. Binding affinities were measured using displacement of 2-[^{125}I]-melatonin at these sites. The agonistic activity of TAK-375 was further tested by measuring it's ability to inhibit forskolin-stimulated cAMP production in Chinese hamster ovary (CHO) cells (8) (Table I).

TAK-375 was shown to have a strong affinity for ML_1 receptors and a low affinity for ML_2 receptors. TAK-375

Table I: Comparison of the in vitro *pharmacological profiles of TAK-375 and melatonin (from Prous Science Integrity®).*

	Melatonin receptor (MT) affinity (K_i, nM)			Agonistic activity[d] (IC_{50}, nM)		
Compound	MT_1	MT_2	MT_3	Rat pituitary gland	Chick forebrain	Human MT_1 receptor
Melatonin	0.082[a] 0.40[c] 0.082	0.2[a] 27.6[b] 28	27.6[b]	0.08	0.043	0.082
TAK-375	0.014[a] 0.025[c] 0.020	0.045[a] 2600[b] 57	2600[b]	0.021 0.098	0.013	0.014

[a]Receptor affinity evaluated by displacement of [^{125}I]-iodomelatonin in CHO cells transfected with human receptor. [b]Receptor affinity evaluated in hamster brain. [c]Receptor affinity evaluated in chick forebrain. [d]Referred to as the ability to inhibit forskolin-induced cAMP production in either rat pituitary gland, chick forebrain or CHO cells transfected with recombinant human MT_1 receptor. (Data from references 3, 9, 15 and 25).

had a higher affinity for ML_1 receptors when compared with melatonin, with a receptor selectivity greater than 1000 times that shown by exogenous melatonin. Moreover, the metabolites of TAK-375 were also been shown to be selective agonists at ML_1 receptor sites. M-II (the most abundant metabolite in human serum) also had a greater binding affinity for ML1 receptors when compared with ML_2 sites. Researchers have reported that this specificity of action limits its potential tolerability profile. Both the parent compound and M-II inhibited cAMP production in CHO cells, further underlining their function as melatonin agonists (8).

The binding affinities of TAK-375 and M-II were also tested at a series of non-ML sites in order to verify their specificity at melatonin receptors. The potential interference of TAK-375 and M-II with a number of enzyme systems and ion channels was also observed. Results showed that both the parent compound and its major metabolite had very weak affinities for other common neurotransmitter receptor sites. Binding affinities at both dopamine and serotonin sites were particularly noted to be low, with respective IC_{50} values of 8.0 μM and 7.2 μM. Authors concluded that as TAK-375 had a reduced affinity for sites involved in cognitive function and abuse liability, the potential for the drug to produce side effects in these ways is subsequently reduced (9, 12).

TAK-375 has been shown to bind specifically and selectively to ML_1 sites in a series of animal models. This potent receptor agonism has also been displayed through efficacy analysis of the sleep-inducing effects of the drug in a number of different studies involving experimental animals.

The effects of TAK-375 on SCN firing patterns were tested in a model involving rat SCN neurons. TAK-375 administration just before the dark cycle induced a phase advance in the circadian rhythm of SCN firing. The phase shift induced by TAK-375 was stronger than that induced by exogenous melatonin administration. TAK-375 was also shown to inhibit the glutamate-induced phase shift, and light-induced phase shift of locomotor activity in these rats (13).

The sleep-promoting effects of TAK-375 (0.1-1 mg/kg p.o.) compared with those of melatonin (1-3 mg/kg p.o.) in an animal model in freely moving cats. Wakefulness was decreased, while slow-wave and REM-sleep were increased following TAK-375 administration. Sleep induction lasted 6 h postadministration. Melatonin also showed sleep-promoting efficacy, but the effects only lasted 2 h postadministration (3, 14).

Investigators further compared the effects of TAK-375 with those of diazepam and triazolam on learning and memory in rats. The Morris water maze and delayed matching positions tests were employed to assess learning and memory in this analysis. Results showed that TAK-375 produced sleep-inducing properties without affecting learning and memory, whereas diazepam and triazolam had significant effects on these parameters (14, 15).

The effects of TAK-375 on motor coordination were compared with melatonin and the ML_2 receptor agonist *N*-acetyl-5-HT, in the rota-rod performance test in mice. Motor performance was decreased via diazepam administration prior to rota-rod performance. TAK-375 had no effect on the benzodiazepine-induced motor dysfunction, while melatonin and *N*-acetyl-5-HT administration exacerbated these symptoms. It was concluded that TAK-375 has no effect on motor dysfunction (a side effect normally encountered following traditional benzodiazepine therapy) (14).

The sleep-inducing effects of TAK-375 were compared with exogenous melatonin and the nonbenzodiazepine hypnotic zolpidem in freely moving monkeys. Female monkeys were entrained to a 12-h light/dark cycle before receiving oral administration of TAK-375 (0.003, 0.03 and 0.3 mg/kg), melatonin (0.3, 1 and 3 mg/kg) or zolpidem (1, 3, 10 and 30 mg/kg). Primary outcome measures were latency to sleep onset and total duration of sleep. Eye movements, EEG recordings and behavior were also measured. Latency to sleep onset was significantly and dose-dependently decreased following TAK-375 administration. Total duration of sleep was increased in these monkeys, particularly time spent in deep sleep (stage III and IV). While melatonin administration also produced a decrease in time to sleep onset,

Table II: Pharmacokinetic profile of TAK-375 after a single oral dose in adult humans and influence of age and gender (20-22).

Dose (mg)	$AUC_{0\rightarrow\infty}$ (μg·h/l)	C_{max} (μg/l)	t_{max} (h)	$t_{1/2}$ (h)	Cl (l/h/kg)
4	1.7	1.1	0.8	0.8	
8	7.0	5.7	0.8	1.4	
16	9.9	6.9	0.8	1.3	
–Young	10.5 [+6.1%]	6.9		1.6 [+23.1%]	
––Male	7.7 [–22.2%]	5.9 [–14.5%]		1.2 [–7.7%]	45.4
––Female	12.5 [+26.3%]	9.5 [+37.7%]		1.3	60.5
–Elderly	18.7 [+88.9%]	11.6 [+68.1%]		2.6 [+100%]	
––Male	17.0 [+71.7%]	12.0 [+73.9%]		1.6 [+23.1%]	22.9
––Female	19.8 [+100%]	11.4 [+65.2%]		2.2 [+69.2%]	23.2
32	22.5	17.4	0.9	1.6	
64	36.1	25.9	0.9	1.9	

$AUC_{0\rightarrow\infty}$, area under concentration-time curve; C_{max}, peak plasma concentration, t_{max}, time to reach peak plasma concentration; $t_{1/2}$ elimination half-life.

the effect was not dose-dependent. Melatonin did not affect total duration of sleep. Zolpidem failed to produce a significant change in either latency to sleep onset or total duration of sleep. TAK-375 produced its effects without causing any changes in behavior or EEG recording, indicating that the sleep induction was quantitatively analogous to spontaneous sleep in this model. This was in contrast to zolpidem administration, which was shown to be associated with EEG changes, as well as sedative and muscle relaxant effects (16-18).

Pharmacodynamics and Pharmacokinetics

The effects of age and gender on TAK-375 pharmacodynamics were tested in a group of 48 healthy volunteers. Subjects were characterized as being young (aged 18-34 years) male (n=12) or female (n=12) and elderly (63-79 years) male (n=12) or female (n=12) for purposes of analysis. Subjects received a single dose of TAK-375 16 mg or placebo on two occasions in this two-way crossover, randomized, double-blind, placebo-controlled trial. Administration of active and placebo treatments were separated by at least 1 week. Objective and subjective measures of sedation were taken to be the primary outcome variables. The digit-symbol substitution test (DSST), word acquisition and recall tests were used to determine psychomotor and memory effects of the medication. All tests were performed at 1 and 24 h postadministration. Age and gender had no effects on the pharmacodynamics of TAK-375 in the young and elderly men or in the young women. Elderly women did show a significant difference in objective measures of sedation and DSST scores. All other variables were comparable between groups, however (19, 20).

The effects of age and gender on TAK-375 and M-II pharmacokinetics were tested in a group of 48 healthy volunteers. Once again, subjects were characterized as being young (aged 18-34 years) male (n=12) or female (n=12) and elderly (63-79 years) male (n=12) or female (n=12). Plasma concentrations of TAK-375 and M-II were analyzed via liquid chromatography mass spectrometry for 24 h following oral administration of a single 16-mg dose of TAK-375. Age had a significant effect on pharmacokinetics, with a higher systemic exposure observed in elderly compared with young subjects (*i.e.*, AUC, C_{max} and $t_{1/2}$ values were significantly increased in elderly subjects). These trends were paralleled in the effects of age on M-II pharmacokinetic parameters. These associations were shown to be independent of gender. Results also showed that TAK-375 had a high oral clearance, with a $t_{1/2}$ of < 3.7 h being reported in all subjects. Less than 5% of TAK-375 and its metabolite M-II was excreted in urine. Individual variability was reported to be high in these volunteers (20, 21) (Table II).

The pharmacokinetics and tolerability of TAK-375 were assessed in a dose-finding study conducted in 60 healthy volunteers aged 35-65 years. Eight subjects each were randomized to receive a single oral dose of TAK-375 4, 8, 16, 32 or 64 mg and 20 subjects were given placebo. DSST scores and a subjective measure of alertness were measured up to 8 h postadministration. TAK-375 was metabolized to M-II (its major metabolite), as well as M-IV, M-I and M-III. Less than 2% of unchanged drug was excreted in the urine. AUC measures were shown to be dose-dependent in TAK-375-treated subjects, with mean values ranging from 1.7-36.1 μg·h/l. C_{max} values showed a similar trend (1.1-25.9 μg/l), whereas t_{max} values were independent of dose. DSST scores and subjective alertness were shown to be independent of dose, indicating the ability of TAK-375 to deliver its pharmacological effect without generating residual cognitive impairment. Nausea and somnolence were the most commonly reported adverse events in this group of healthy volunteers (22).

Clinical Studies

The efficacy and tolerability of TAK-375 were evaluated in a phase II study in 375 healthy volunteers employing a first night effect model of transient insomnia.

Table III: Clinical studies of TAK-375 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Insomnia	Randomized, double-blind	TAK-375, 4 mg po od (n=8) TAK-375, 8 mg po od (n=8) TAK-375, 16 mg po od (n=8) TAK-375, 32 mg po od (n=8) TAK-375, 64 mg po od (n=8) Placebo (n=20)	60	Single oral doses of up to 64 mg of TAK-375 were well tolerated and only induced mild to moderate adverse effects	22
Insomnia	Randomized, double-blind, multicenter	TAK-375, 16 mg po sd (n=126) TAK-375, 64 mg po sd (n=126) Placebo (n=123)	375	A single dose of 16 mg of TAK-375 was significantly more effective than placebo in reducing the latency to persistent sleep and increasing the mean total sleep time of patients with transient insomnia	23
Insomnia	Randomized, double-blind, crossover	TAK-375, 4 mg po od x 2 [consecutive nights] TAK-375, 8 mg po od x 2 [consecutive nights] TAK-375, 16 mg po od x 2 [consecutive nights] TAK-375, 32 mg po od x 2 [consecutive nights] Placebo	107	Compared with placebo, TAK-375 at oral doses ranging from 4-32 mg significantly reduced the latency to persistent sleep and increased the mean total sleep time and the sleep efficiency of patients with chronic insomnia. The drug was well tolerated and had no adverse effects on memory recall or on post-sleep alertness and ability to concentrate	24

Subjects were randomized to receive a single oral dose of TAK-375 (16 or 64 mg) or placebo in this multicenter, double-blind, placebo-controlled trial. Subjects were instructed to take the medication 30 min before their normal bedtime and were monitored for 8 h postadministration by polysomnography. The primary outcome variables were latency to persistent sleep (LPS) and total sleep time (TST). Subjective measures of LPS and TST were also measured. Subjective measures of alertness and concentration, as well as the DSST were calculated on waking to ascertain any residual sedative effects of the study drug. Results showed that mean LPS was significantly shorter in the TAK-375 16-mg and 64-mg groups as compared to placebo (12.2 and 13.4 min *vs.* 22.6 min). These differences were not dose-dependent, however. Mean TST was significantly longer in both active treatment groups as compared to placebo (427.3 and 424.7 min *vs.* 413.3 min). Time spent in the different stages of sleep was comparable between groups. Subjective LPS and TST scores were significantly different from placebo in the TAK-375 16 mg group but not the TAK-375 64 mg group. Subjective measures of alertness and concentration indicated a possible residual sedative effect in the TAK-375 64 mg group, although DSST measures did not. Vital signs and ECG recordings were comparable between groups. The most commonly reported adverse events were headache, somnolence, fatigue, nausea and dizziness (23). The results of this study and the one that follows are summarized in Table III.

The efficacy and tolerability of TAK-375 were further evaluated in a randomized, double-blind, placebo-controlled, phase II study in 107 patients (18-64 years) with primary chronic insomnia. Primary chronic insomnia was diagnosed according to standard DSM-IV criteria (presence of insomnia for > 3 months, mean LPS > 20 min and mean wake time > 60 min for 2 consecutive nights). TAK-375 was administered 30 min prior to habitual bedtime at doses of 4, 8, 16 and 32 mg for 2 consecutive nights. Primary outcome variables were objective and subjective measures of LPS, TST and sleep efficiency. Time spent in the different stages of sleep was also assessed. Residual sedation was calculated by performing DSST, memory recall and subjective assessments of alertness and concentration on awakening. Objective measures of LPS were significantly decreased in all TAK-375 dosing groups when compared with placebo. Subjective measures of LPS were also significantly shorter in the TAK-375 16 mg recipients. The association was not apparent in other active treatment groups, however. TST and sleep efficiency were significantly increased in all groups compared with placebo. Total time in NREM sleep was significantly lower in active treatment groups compared with placebo. Subjective TST and sleep quality measures were comparable among groups. Post-sleep test scores were also comparable among groups, indicating a lack of residual pharmacological effects. Adverse event rates were also comparable among groups, with the most commonly reported events being headache (19.6%), pharyngeal pain (7.5%) and somnolence (7.5%). All adverse events were said to be of mild to moderate intensity (24) (Figs. 1 and 2).

Conclusions

TAK-375 is a promising new drug candidate for the treatment of sleep disorders. Exhibiting specific and selective action at the ML_1 receptor, TAK-375 is highly

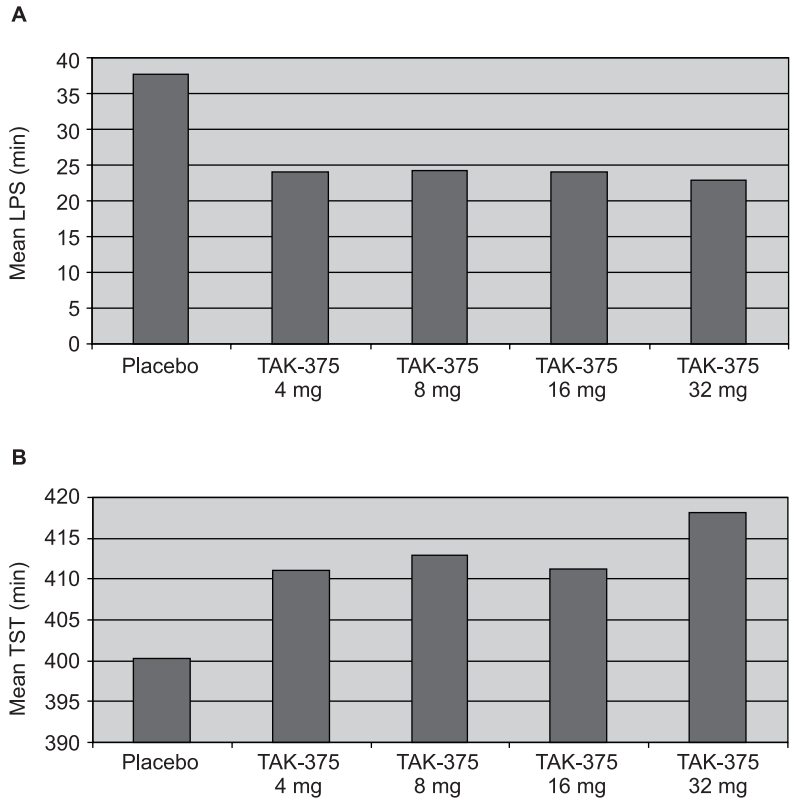


Fig. 1. Efficacy of TAK-375 on outcome measures of latency to persistent sleep (A) and total sleep time (B) in patients with primary chronic insomnia (24).

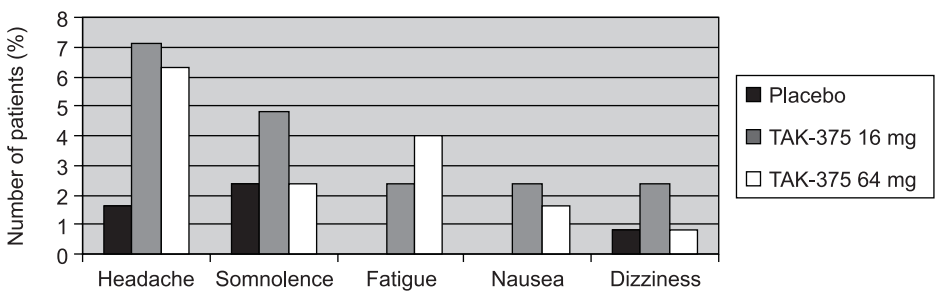


Fig. 2. Adverse events associated with TAK-375 in patients with primary chronic innnsomnia (24).

effective in its ability to induce sleep, yet is not associated with the plethora of side effects encountered following melatonin administration. Phase III trials are currently under way to test the viability of TAK-375 for use in patients with sleep disorders.

Source

Takeda Chemical Industries, Ltd. (JP).

References

1. Miyamoto, M., Ohkawa, S., Uchikawa, O., Fukatsu, K. (Takeda Chemical Industries, Ltd.). *Tricyclic cpds., their production and use.* EP 0885210, JP 1998287665, JP 1999152281, WO 9732871.

2. Ohkawa, S. *Discovery of the novel melatonin agonist TAK-375.* 22nd Symp Med Chem (Nov 27-29, Shizuoka) 2002, Abst IL 11.

3. Uchikawa, O., Fukatsu, K., Tokunoh, R. et al. *Synthesis of a novel series of tricyclic indan derivatives as melatonin receptor agonists.* J Med Chem 2002, 45: 4222-39.

4. Perreau-Lenz, S., Kalsbeek, A., Garidou, M.L., Wortel, J., van der Vliet, J., van Heijningen, C., Simonneaux, V., Pevet, P., Buijs, R.M. *Suprachiasmatic control of melatonin synthesis in rats: Inhibitory and stimulatory mechanisms.* Eur J Neurosci 2003, 17: 221-8.

5. Zisapel, N. *Circadian rhythm sleep disorders: Pathophysiology and potential approaches to management.* CNS Drugs 2001, 15: 311-28.

6. Monti, J.M., Cardinali, D.P. *A critical assesment of the melatonin effect on sleep in humans.* Biol Signals Recept 2000, 9: 328-39.

7. Karasek, M., Reiter, R.J., Cardinali, D.P., Pawlikowski, M. *Future of melatonin as a therapeutic agent.* Neuroendocrinol Lett 2002, 23(Suppl. 1): 118-21.

8. Hirai, K., Kato, K., Nishiyama, H., Hinuma, S., Uchikawa, O., Ohkawa, S., Miyamoto, M. *TAK-375 and its metabolites are selective agonists at MLs1s receptors.* Sleep 2003, 26(Suppl.): Abst 0193.C.

9. Kato, K., Uchikawa, O., Fukatsu, K., Ohkawa, S., Miyamoto, M. *Neuropharmacological properties of TAK-375, a novel ML_1-selective melatonin receptor agonist.* Int J Neuropsychopharmacol, 2000. 3(Suppl. 1): Abst P.03.130.

10. Liu, C., Weaver, D., Jin, X., Shearman, L., Pieschl, R., Gribkoff, V., Reppert, S.M. *Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock.* Neuron 1997, 19: 91-102.

11. Vanecek, J. *Cellular mechanisms of melatonin action.* Physiol Rev 1998, 78: 687-721.

12. Miyamoto, M., Kato, K., Hirai, K., Uchikawa, O., Ohkawa, S. *TAK-375 and its active metabolite: Lack of binding to non-ML receptor binding sites.* Sleep 2003, 26(Suppl.): Abst 0194.C.

13. Inoue, S., Shimazoe, T., Moriya, T., Shinohara, K., Miyamoto, M., Watanabe, S. *Effects of TAK-375, a novel ML_1-selective melatonin receptor agonist, on entrainment function in circadian rhythm.* 76th Annu Meet Jpn Pharmacol Soc(March 24-26, Fukuoka) 2003, Abst 3D0854.

14. Miyamoto, M., Nishikawa, H., Ohta, H., Hirai, K., Uchikawa, O., Fukatsu, K., Ohkawa, S. *Pharmacological effects of TAK-375, a ML_1-selective melatonin receptor agonist, in experimental animals.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.03.125.

15. Fukatsu, K., Uchikawa, O., Kato, K., Nishikawa, H., Hinuma, S., Miyamoto, M., Ohkawa, S. *Synthesis and sleep promoting action of TAK-375, a novel melatonin agonist.* 20th Symp Med Chem (Dec 6-8, Tokyo) 2000, Abst 1P-28.

16. Yukuhiro, N., Kimura, H., Nishikawa, H., Ohkawa, S., Miyamoto, M. *Effects of TAK-375, a novel melatonin receptor agonist, on sleep in freely moving monkeys.* Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.03.127.

17. Yukuhiro, N., Nishikawa, H., Kimura, H., Ohkawa, S., Miyamoto, M. *Sleep in freely moving monkeys: Comparison of TAK-375, melatonin, and zolpidem.* Sleep 2003, 26(Suppl.): Abstract 0195.C.

18. Yukuhiro, N., Nishikawa, H., Kimura, H., Ohkawa, S., Miyamoto, M. *Effects of TAK-375, a novel melatonin receptor agonist, on sleep in freely moving monkeys at nighttime.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-791.

19. Greenblatt, D.J., Harmatz, J.S. *Effect of age and gender on the pharmacodynamics of TAK-375: Tests of sedation, psychomotor function, and memory.* Sleep 2003, 26(Suppl.): Abst 0197.C.

20. Greenblatt, D.J., Harmatz, J.S., Stubbs, C. *Effect of age on the pharmacokinetics and pharmacodynamics of TAK-375: A novel selective ML-1 receptor agonist under investigation for the treatment of insomnia.* 11th Int Congr Int Psychogeriatr Assoc (Aug 17-22, Chicago) 2003, Abst PA-015.

21. Greenblatt, D.J. Harmatz, J.S. *Age and gender effects on the pharmacokinetics of TAK-375.* Sleep 2003, 26(Suppl.): Abst 0198.C.

22. Stubbs, C., Karim, A. *A safety, tolerance, and pharmacokinetic study of five single doses of TAK-375 in healthy adults.* Sleep 2003, 26(Suppl.): Abst 0187.C.

23. Roth, T., Walsh, J. *Phase II study of the selective ML-1 receptor agonist TAK-375 in a first night effect model of transient insomnia.* Sleep 2003, 26(Suppl.): Abst 0739.L.

24. Erman, M., Seiden, D., Zammit, G. *Phase II study of the selective ML-1 receptor agonist TAK-375 in subjects with primary chronic insomnia.* Sleep 2003, 26(Suppl.): Abst 0748.L.

25. Ohkawa, S., Uchikawa, O., Fukatsu, K., Tokunoh, R., Kawada, M., Matsumoto, K., Imai, Y., Kato, K., Nishikawa, H., Miyamoto, M. *Synthesis of a novel series of tricyclic indan derivatives as melatonin agonists.* 16th Int Symp Med Chem (Sept 18-22, Bologna) 2000, Abst PB-108.

Additional References

Tarui, N., Nagano, Y., Sakane, T., Matsumoto, K., Kawada, M., Uchikawa, O., Ohkawa, S., Nakahama, K. *Kinetic resolution of an indan derivative using Bacillus sp. SUI-12: Synthesis of a key intermediate of the melatonin receptor agonist TAK-375.* J Biosci Bioeng 2002, 93: 44-7.

Miyamoto, M., Kato, K., Hirai, K., Uchikawa, O., Ohkawa, S. *TAK-375 and its active metabolite: Lack of binding to non-ML receptor binding sites.* 11th Int Congr Int Psychogeriatr Assoc (Aug 17-22, Chicago) 2003, Abst PA-028.

Kato, K., Hirai, K., Uchikawa, O., Fukatsu, K., Ohkawa, S., Hinuma, S., Miyamoto, M. *Neuropharmacological properties of TAK-375, a novel melatonin ML_1 receptor agonist.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-790.

Miyamoto, M., Nishikawa, H., Hirai, K., Ohta, H., Uchikawa, O., Fukatsu, K., Ohkawa, S. *Sleep-promoting action and pharmacological effects of TAK-375, a novel ML_1-selective melatonin receptor agonist, in experimental animals.* Jpn J Pharmacol 2001, 85(Suppl. I): Abst P-792.