Drugs of the Future 2008, 33(3): 206-212

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.03.1185054

Taranabant

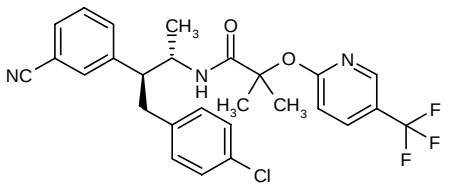
Prop INN; USAN

Cannabinoid CB_1 Inverse Agonist
Antiobesity Drug

MK-0364

N-[3-(4-Chlorophenyl)-2(*S*)-(3-cyanophenyl)-1(*S*)-methylpropyl]-2-methyl-2-[5-(trifluoromethyl)pyridin-2-yloxy]propionamide

InChI=1/C27H25ClF3N3O2/c1-17(34-25(35)26(2,3)36-24-12-9-21(16-33-24)27(29,30)31)23(14-18-7-10-22(28)11-8-18)20-6-4-5-19(13-20)15-32/h4-13,16-17,23H,14H2,1-3H3,(H,34,35)/t17-,23+/m0/s1



$C_{27}H_{25}ClF_3N_3O_2$
Mol wt: 515.9543

CAS: 701977-09-5

CAS: 605678-99-7 (racemate)

CAS: 701977-00-6 (stereoisomer)

CAS : 701977-08-4 (diastereomer)

EN: 427829

Abstract

The cannabinoid CB_1 receptor, a G-protein-coupled receptor expressed in the nervous system, has been linked to the control of food intake and energy expenditure in a variety of studies. The CB_1 receptor inverse agonist rimonabant (Acomplia®) has proven to decrease food intake and increase energy expenditure and weight loss in animal models and humans, and the drug has been approved for the treatment of obesity in Europe. Taranabant (MK-0364) is a structurally novel CB_1 receptor inverse agonist under development for the treatment of obesity that has demonstrated promising activity in preclinical studies, including inhibition of food intake and body weight gain in rodents with diet-induced obesity, effects not seen in CB_1 receptor-deficient mice. Early clinical trials have also revealed reduced food intake and increased energy expenditure with taranabant in overweight and obese subjects. Phase II trials in overweight and obese individuals are under way, with the results of one 12-week study showing dose-related body weight loss compared to placebo but an increase in psychiatric-related adverse events at higher doses. Further data are needed to determine if these events can be avoided at effective doses, a possibility held forth by the finding that efficacy in terms of weight loss does not require complete CB_1 receptor occupancy.

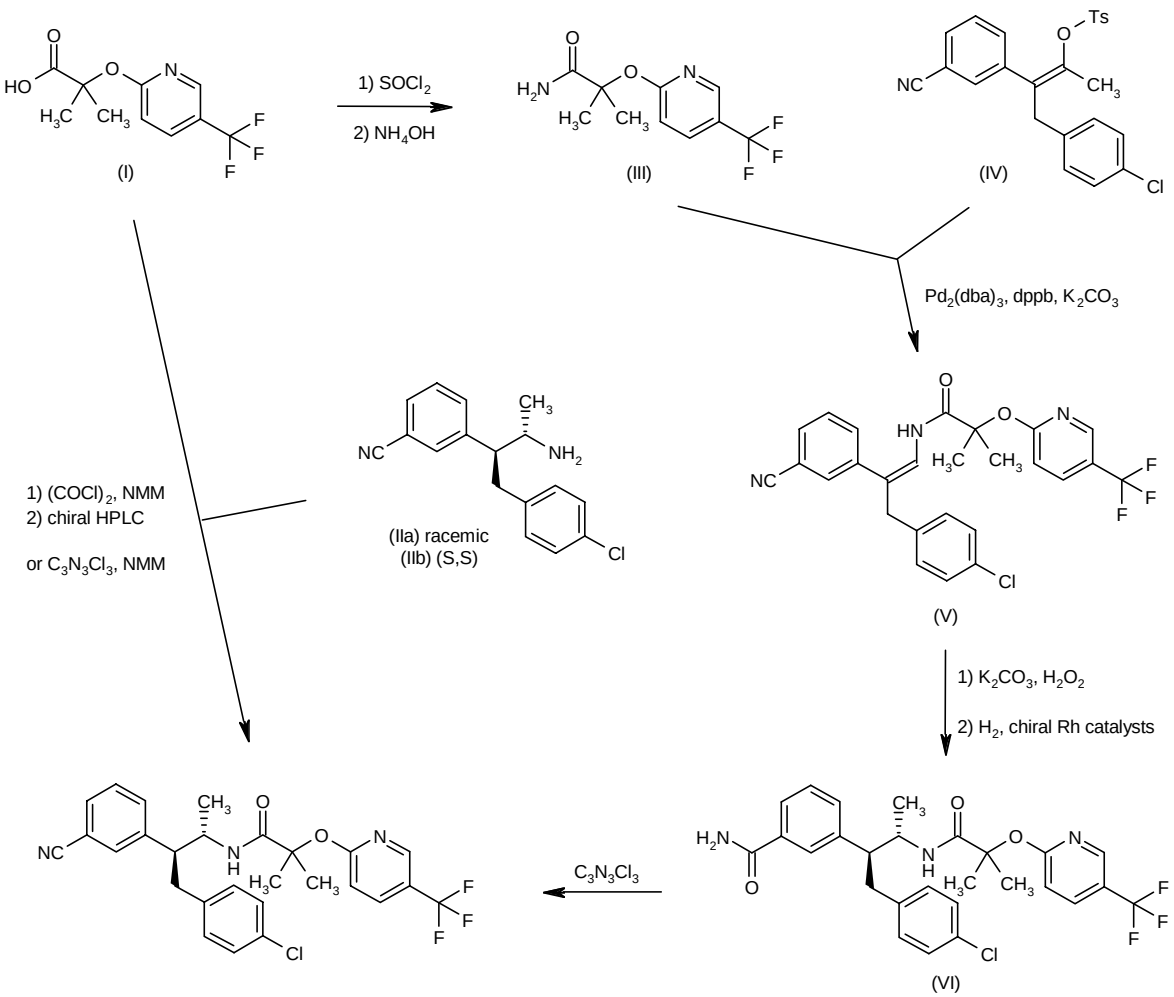
Synthesis

Taranabant can be prepared by two different synthetic strategies. 2-Methyl-2-[5-(trifluoromethyl)pyridin-2-yloxy]propionic acid (I) is chlorinated with oxalyl chloride and DMF in CH_2Cl_2, and the resulting acid chloride is then coupled with 3-(4-chlorophenyl)-2(*R,S*)-(3-cyanophenyl)-1(*R,S*)-methylpropylamine (IIa) by means of NMM in CH_2Cl_2 to produce racemic taranabant, which is finally resolved employing chiral HPLC (1-3). Similarly, the target enantiomer is obtained by condensation of acid (I) with the (*S,S*)-amine (IIb) using cyanuric chloride and NMM as the coupling reagents (4). In an alternative method, acid (I) is converted to the carboxamide (III) by chlorination with $SOCl_2$ followed by treatment with ammonium hydroxide. Subsequent coupling of amide (III) with the enol tosylate (IV) in the presence of $Pd_2(dba)_3$ and 1,4-bis(diphenylphosphino)butane (dppb) gives the *N*-acyl enamine (V). After hydrolysis of the cyano group to the corresponding carboxamide with K_2CO_3 and H_2O_2, asymmetric hydrogenation of the enamine double bond over chiral rhodium catalysts (generated from a diene-rhodium complex salt and chiral diphosphine ligands) provides the desired isomer (VI). Reconversion of carboxamide (VI) to the target nitrile is finally accomplished by treatment with cyanuric chloride in DMF/MTBE (5, 6). Scheme 1.

Intermediates (II) and (IV) are prepared as follows. Alkylation of the sodium enolate of methyl 3-bromophenylacetate (VII) with 4-chlorobenzyl bromide (VIII) in cold THF followed by methyl ester hydrolysis with LiOH in aqueous acetonitrile affords 2-(*m*-bromophenyl)-3-(*p*-chlorophenyl)propionic acid (IX), which is converted to the corresponding Weinreb amide (X) by chlorination with oxalyl chloride and subsequent treatment with *N,O*-dimethylhydroxylamine. Addition of methylmagnesium bromide to the methoxyamide (X) gives the 3,4-diaryl-2-butanone (XI), which is then reduced using $NaBH_4$ or $LiBH(s\text{-}Bu)_3$ (L-selectride) to provide alcohol (XIIa) as the major diastereoisomer. After conversion of alcohol (XIIa)

P. Cole, N. Serradell, E. Rosa, J. Bolós. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

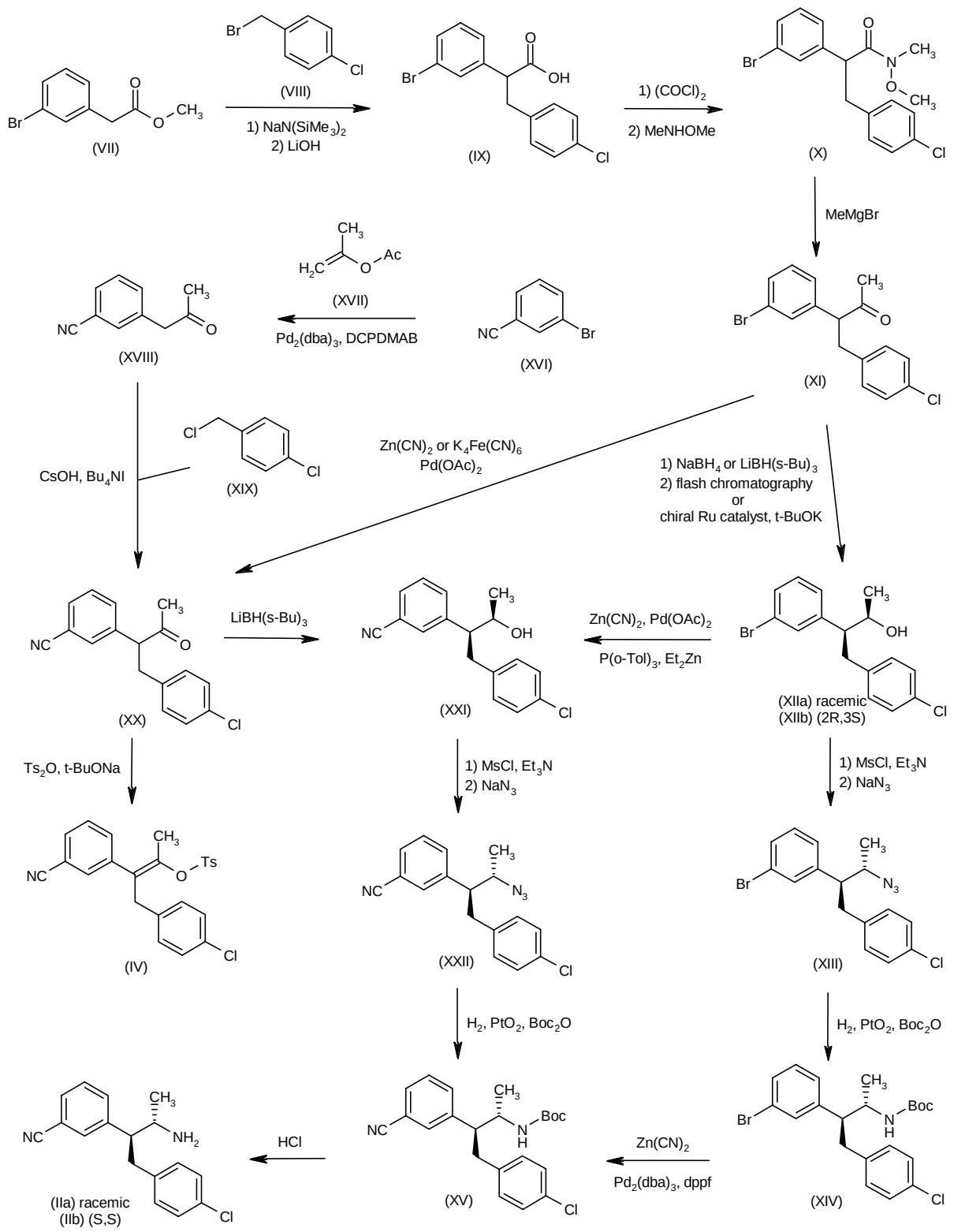
Scheme 1: Synthesis of Taranabant



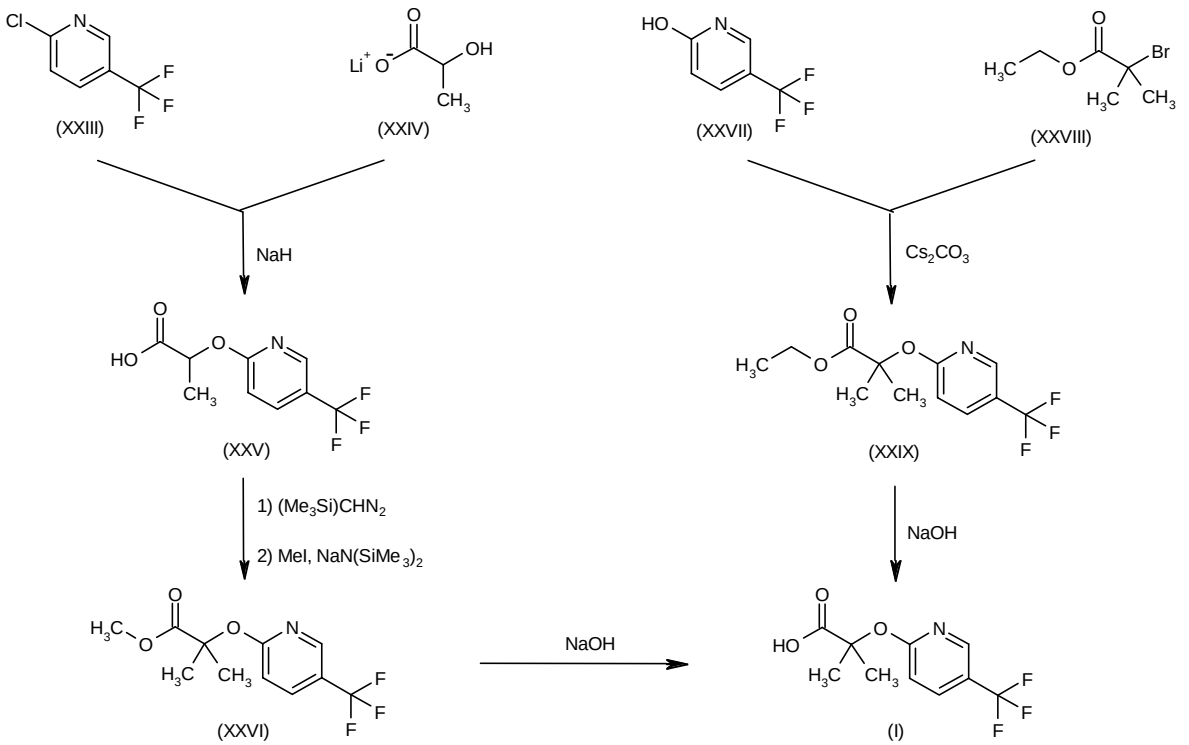
to the corresponding mesylate, displacement with NaN_3 in hot DMF leads to azide (XIII), which is reduced by catalytic hydrogenation in the presence of PtO_2 and Boc_2O to afford the Boc-protected amine (XIV). Then, palladium-catalyzed substitution of the aryl bromide (XIV) with zinc cyanide yields the nitrile (XV), which is deprotected to (IIa) using HCl in EtOAc (2, 3). Similarly, coupling between 3-bromobenzonitrile (XVI) and isopropenyl acetate (XVII) in the presence of $Pd_2(dba)_3$ and 2-(dicyclohexylphosphino)-2'-(dimethylamino)biphenyl (DCPDMAB) gives 1-(*m*-cyanophenyl)acetone (XVIII), which is alkylated with 3-chlorobenzyl chloride (XIX) in the presence of cesium hydroxide and tetrabutylammonium iodide to yield the diarylbutanone (XX). Reduction of ketone (XX) with lithium tri(*sec*-butyl)borohydride produces alcohol (XXI), which is converted to the Boc-protected amine (XV) by mesylation followed by displacement with NaN_3, and then reduction of the resulting azide (XXII) by catalytic hydrogenation in the presence of PtO_2 and Boc_2O (1). The ketonitrile (XX) is alternatively produced by palladium-catalyzed cyanuration of aryl bromide (XI) with either zinc cyanide or potassium ferrocyanide. The intermediate enol tosylate (IV) can be obtained by treatment of (XX) with sodium *tert*-butoxide and *p*-toluenesulfonic anhydride (5, 6). Preparation of the enantiomerically pure amine (IIb) can be accomplished by resolution at the stage of the diarylpropionic acid (IX) or, in a more efficient method, by dynamic kinetic resolution of (XI) via stereoselective hydrogenation to (XIIb) in the presence of the chiral Ru catalyst [(*S*)-*xyl*-BINAP]-[(*S*)-DAIPEN]$RuCl_2$ and excess potassium *tert*-butoxide (4). Scheme 2.

Two procedures have been reported for the synthesis of the intermediate 2-methyl-2-[5-(trifluoromethyl)pyridin-2-yloxy]propionic acid (I). 2-Chloro-5-(trifluoromethyl)pyridine (XXIII) is coupled with lithium lactate (XXIV) employing NaH in hot DMF to produce the 2-(pyridyloxy)propionic acid (XXV). After esterification of acid (XXV) with

Scheme 2: Synthesis of Intermediates (II) and (IV)



Scheme 3: Synthesis of Intermediate (I)



trimethylsilyldiazomethane in $MeOH/CH_2Cl_2$, the resulting methyl ester is alkylated with iodomethane and sodium hexamethyldisilazide to furnish the (pyridyloxy)isobutyrate (XXVI). Subsequent hydrolysis of methyl ester (XXVI) with NaOH in H_2O/MeOH/THF provides the target carboxylic acid intermediate (I) (1). Alternatively, the condensation of 2-hydroxy-5-(trifluoromethyl)pyridine (XXVII) with ethyl 2-bromoisobutyrate (XXVIII) in the presence of cesium carbonate provides the 2-(pyridyloxy)isobutyrate ester (XXIX), which is hydrolyzed to the corresponding carboxylic acid (I) by means of NaOH in acetonitrile/water (2, 3). Scheme 3.

Background

Obesity has been classified as a global epidemic (7), and its prevalence is increasing across age groups throughout the industrialized world (8). Obesity is associated with a wide array of co-morbid conditions, notably diabetes, coronary heart disease and hypertension. As it increases the risk of other health disorders, obesity has a similar severe impact on mortality, with a 50-100% increased risk of death from all causes in obese subjects as compared with normal-weight individuals of the same age (9, 10). The direct and indirect costs of obesity and diseases secondary to obesity are staggering, reaching USD 117 billion for 1999-2000 in the United States, with USD 61 billion being direct costs (11).

As long-term compliance to diet and exercise plans is low, many patients require pharmacotherapy to lose weight. Existing monotherapies are able to achieve a maximum average weight loss of about 10% after approximately 6 months of use, although weight is often regained when drug therapy is discontinued (12).

Several lines of evidence implicate the cannabinoid CB_1 receptor and endogenous agonists, or endocannabinoids, in the modulation of food intake and energy expenditure. Studies in different species have shown the CB_1 receptor to be expressed in various brain regions, including the hypothalamus, amygdala, hippocampus, basal ganglia, cortex and cerebellum, and some of these areas have been implicated in food intake and energy balance (13-16). The CB_1 receptor is the brain receptor for tetrahydrocannabinol, the psychoactive substance in marijuana, and marijuana use is associated with increased appetite (13, 17). Cannabinoid agonists have been shown to increase the reward value of food, while the CB_1 receptor inverse agonist rimonabant has been found to inhibit the intake of food in lean rodents and rodents with diet-induced obesity, marmosets and humans (18-23). Inverse agonists have also been shown to increase energy expenditure (24). Leptin, derived from adipocytes,

appears to modulate the levels of endocannabinoids (22). Finally, CB_1 receptor knockout in mice was associated with a lean phenotype and resistance to diet-induced obesity (25).

Rimonabant (Acomplia®) was approved in Europe in 2006 for the treatment of obesity. It has been associated with weight loss but also with side effects, particularly an increased risk of psychiatric adverse events (26).

Investigators at Merck Research Laboratories discovered a number of novel acyclic amide CB_1 receptor inverse agonists which proved to be potent, selective and orally bioavailable. Optimization efforts intended to enhance *in vivo* efficacy and reduce the potential for the formation of reactive metabolites led to the identification of taranabant (MK-0364), a structurally distinct compound from rimonabant, which has demonstrated beneficial effects on food intake and body weight in preclinical studies and is currently undergoing clinical investigation in obese subjects (3, 27).

Preclinical Pharmacology

In binding assays utilizing the cannabinoid receptor agonist [^{3}H]-CP-55940, taranabant was found to bind to the recombinant human CB_1 receptor with an IC_{50} of 0.3 nM and to the rat CB_1 receptor with an IC_{50} of 0.4 nM, with corresponding K_i values of 0.13 and 0.27 nM. The IC_{50} values for binding to human and rat CB_2 receptors were 290 and 470 nM, respectively, with corresponding K_i values of 170 and 310 nM. Taranabant showed over 1,000-fold selectivity for CB_1 receptors over CB_2 receptors and numerous other targets. Taranabant also demonstrated inverse agonist activity at the CB_1 receptor, having the opposite effect (a further increase) on forskolin-induced cAMP levels than CP-55940 in CB_1 receptor-expressing Chinese hamster ovary (CHO) cells (EC_{50} = 2 nM) (3, 27).

In rats with diet-induced obesity, acute administration of taranabant 1 and 3 mg/kg p.o. dose-dependently inhibited food intake (60% and 70%, respectively, at 6 h) and body weight gain, effects not seen in CB_1 receptor-deficient mice. At a minimum effective dose of 0.3 mg/kg, chronic administration was associated with decreased food intake, body weight gain and adiposity in diet-induced obese rats treated for 2 weeks. The relative weight loss compared with vehicle for doses of 0.3, 1 and 3 mg/kg was 4%, 5% and 7%, respectively, at the end of the study. Single taranabant doses of 0.3, 1, 3, 10 and 30 mg/kg p.o. were associated with dose-dependent increases in CB_1 receptor occupancy in rats. When the chronic administration study was repeated, brain CB_1 receptor occupancy by taranabant of 30% at 2 h postdose was associated with weight loss, and higher occupancy was correlated with greater efficacy. Furthermore, cumulative weight gain, body composition, cumulative food intake and cumulative feed efficiency in heterozygous mice with one disrupted allele of the CB_1 receptor gene *Cnr1* were intermediate between wild-type and CB_1 receptor-deficient mice, further supporting the notion of partial receptor occupancy by taranabant being associated with efficacy in terms of weight loss (27-29).

Safety

The results of a phase II study comparing taranabant and placebo in obese patients (NCT00109148) revealed a risk of psychiatric adverse events with higher doses. The randomized, double-blind, multicenter trial included 533 patients given placebo or taranabant 0.5, 2, 4 or 6 mg/day for 12 weeks. In these groups, the percentage of patients discontinuing due to adverse events was 10.5%, 4.7%, 4.6%, 16.2% and 10.2%, respectively. Gastrointestinal events were significantly increased in the higher taranabant dose groups, to 61.0% and 53.7% on 4 and 6 mg, respectively, compared to placebo (38.1%). Psychiatric adverse events were also significantly increased in the taranabant 2, 4 and 6 mg groups (27.5%, 31.4% and 27.8%, respectively) compared to placebo (18.1%). Of the psychiatric adverse events, the incidence of anxiety was significantly higher in the taranabant 6 mg group (10.2%) compared to placebo (2.9%). Psychiatric-related adverse events led to treatment discontinuation in 15% of patients. The similarity of the psychiatric adverse events seen in this study and in studies of rimonabant –depression, anxiety, irritability and others– suggest that the events may be related to the agents' mechanism of action (30).

Clinical Studies

A randomized, double-blind, placebo-controlled study in 15 healthy, lean male volunteers was conducted to determine human brain CB_1 receptor occupancy after single and multiple doses of taranabant. Study subjects received 14 days of treatment with placebo or taranabant 1, 4 or 7.5 mg, or a single taranabant dose of 12 mg followed by multiple doses of 6 mg. Brain CB_1 receptor occupancy was assessed by PET with the CB_1 receptor ligand [^{18}F]-MK-9470 before dosing and at approximately 2 and/or 24 h after single or multiple doses. The results revealed dose-dependent occupancy of brain CB_1 receptors after single and multiple doses. A plasma concentration of taranabant of 7 nM was required to achieve an average target brain CB_1 receptor occupancy of 30% at 24 h, and this level of occupancy was achieved with doses of 4-6 mg/day. The treatment was generally well tolerated (30-32).

The weight loss seen with CB_1 receptor inverse agonists appears to be due in part to increases in energy expenditure, as shown in a randomized, double-blind, 4-period crossover study in overweight and moderately obese male subjects. The 17 subjects included in the study received single doses of placebo, taranabant 4 mg, taranabant 12 mg and sibutramine 30 mg, and resting energy expenditure (REE) was evaluated using indirect calorimetry over a 5-h postdose period and at 24 h postdose. Peak REE was the maximum of the average of two consecutive 30-min measurements within 2-5 h postdose.

Peak REE geometric mean ratios for taranabant 4 mg, taranabant 12 mg and sibutramine 30 mg *versus* placebo were 1.02, 1.06 and 1.03, respectively. Taranabant and sibutramine were generally well tolerated (33, 34).

The reductions in food (energy) intake seen with taranabant in preclinical studies have also been seen in overweight humans, indicating that this is also a mechanism by which the drug reduces weight. The effect of taranabant on food intake was investigated in a randomized, double-blind, placebo-controlled, 4-period crossover study in 36 overweight/obese male subjects. The treatments were the same as in the above study, with placebo, taranabant 4 and 12 mg and sibutramine 30 mg as positive control. The subjects received meals at 3, 10, 13 and 24 h postdose that were approximately 5 times larger than standard portions and could be consumed *ad libitum*. Analysis of caloric intake showed mean reductions in energy intake over 24 h of 3%, 22% and 12% with taranabant 4 mg, taranabant 12 mg and sibutramine 30 mg, respectively, compared to placebo. Taranabant 12 mg and sibutramine 30 mg significantly reduced energy intake by approximately 27% and 20%, respectively, at the lunch meal compared to placebo. Energy intake was lowest with taranabant 12 mg at all four meals. The effect of taranabant 4 mg on energy intake was not significant. Taranabant and sibutramine were again well tolerated (35, 36).

Data from the phase II study discussed above (NCT00109148) showed reduced body weight with taranabant in obese subjects. In an analysis using last observation carried forward to impute missing data, least-squares mean changes from baseline in body weight were –1.2, –2.9, –3.9, –4.1 and –5.3 kg, respectively, with placebo and taranabant doses of 0.5, 2, 4 and 6 mg, representing a significant trend over the range of study doses. A significant dose-response effect was also seen for the change in waist circumference (30).

A number of other studies of the effect of taranabant on weight are presently ongoing. These include three randomized, double-blind, placebo-controlled phase II studies in obese and overweight subjects, a phase II study of weight loss in patients with type 2 diabetes and a phase III study in obese patients (37-41). A phase II trial is also under way investigating taranabant as an aid to smoking cessation (42).

Drug Interactions

Chronic administration of taranabant did not appear to alter the pharmacokinetics of ethinylestradiol or norelgestromin in a study in healthy women taking the oral contraceptive Ortho Tri-Cyclen®. The randomized, crossover study included two 28-day contraceptive cycles wherein 19 healthy female volunteers with normal menstrual cycles received active oral contraceptive for 21 days followed by 7 days of placebo. On days 1-21 of each cycle, subjects were given a single dose of oral taranabant 6 mg or placebo. Evaluation of plasma samples on day 21 of each 28-day cycle revealed geometric mean ratios for ethinylestradiol and norelgestromin of 0.93 and 1.02, respectively, for AUC_{0-24} and 0.95 and 0.95, respectively, for C_{max}. These values were within predefined acceptable boundaries of bioequivalence. Co-administration of taranabant and oral contraceptive was generally well tolerated, with only mild adverse events observed and none leading to discontinuation. Headache and nausea were the most common drug-related adverse events (43).

Source

Merck & Co., Inc. (US).

References

1. Hagmann, W.K., Lin, L.S., Shah, S.K. et al. (Merck & Co., Inc.). *Substituted amides*. CA 2478183, EP 1496838, JP 2005519958, JP 2006257090, US 2004058820, US 6972295, WO 03077847.

2. Hagmann, W.K., Lin, L.S., Shah, S.K. et al. (Merck & Co., Inc.). *Substituted amides active at the cannabinoid-1 receptor*. WO 2004048317.

3. Lin, L.S., Lanza, T.J. Jr., Jewell, J.P. et al. *Discovery of N-[(1S,2S)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-[[5-(trifluoromethyl)pyridin-2-yl]oxy]propanamide (MK-0364), a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity*. J Med Chem 2006, 49(26): 7584-7.

4. Chen, C., Frey, L.F., Shultz, S. et al. *Catalytic, enantioselective synthesis of taranabant, a novel, acyclic cannabinoid-1 receptor inverse agonist for the treatment of obesity*. Org Proc Res Devel 2007, 11(3): 616-23.

5. Campos, K.R., Klapars, A., McWilliams, J.C. et al. (Merck & Co., Inc.). *Formation of tetra-substituted enamides and stereoselective reduction thereof*. WO 2006017045.

6. Weissman, S.A. (Merck & Co., Inc.). *Cyanation of aromatic halides*. US 2006106223.

7. Smyth, S., Heron, A. *Diabetes and obesity: The twin epidemics*. Nat Med 2006, 12(1): 75-80.

8. Ogden, C.L. et al. *Prevalence of overweight and obesity in the United States, 1999-2004*. JAMA - J Am Med Assoc 2006, 295(13): 1549-55.

9. Allison, D.B. et al. *Annual deaths attributable to obesity in the United States*. JAMA - J Am Med Assoc 1999, 282(16): 1530-8.

10. Poirier, P. et al. *Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss: An update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism*. Circulation 2006, 113(6): 898-918.

11. U.S. Department of Health and Human Services. *The Surgeon General's call to action to prevent and decrease overweight and obesity*. U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.

12. Bray, G.A., Greenway, F.L. *Pharmacological treatment of the overweight patient*. Pharmacol Rev 2007, 59(2): 151-84.

13. Breivogel, C.S., Childers, S.R. *The functional neuroanatomy of brain cannabinoid receptors*. Neurobiol Dis 1998, 5(6, Pt. B): 417-31.

14. Berthoud, H.R. *Multiple neural systems controlling food intake and body weight*. Neurosci Biobehav Rev 2002, 26(4): 393-428.

15. Seeley, R.J., Woods, S.C. *Monitoring of stored and available fuel by the CNS: Implications for obesity*. Nat Rev Neurosci 2003, 4(11): 901-9.

16. Schwartz, M.W., Porte, D. Jr. *Diabetes, obesity, and the brain*. Science 2005, 307(5708): 375-9.

17. Greenberg, I. Kuehnle, J., Mendelson, J.H., Bernstein, J.G. *Effects of marihuana use on body weight and caloric intake in humans*. Psychopharmacology 1976, 49(1): 79-84.

18. Gardner, E.L., Vorel, S.R. *Cannabinoid transmission and reward-related events*. Neurobiol Dis 1998, 5(6): 502-33.

19. Arnone, M., Maruani, J., Chaperon, F., Thiébot, M-H., Poncelet, M., Soubrié, P., Le Fur, G. *Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors*. Psychopharmacology 1997, 132(1): 104-6.

20. Simiand, J., Keane, M., Keane, P.E., Soubrie, P. *SR141716, a CB1 cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset*. Behav Pharmacol 1998, 9(2): 179-81.

21. Freedland, C.S., Poston, J.S., Porrino, L.J. *Effects of SR141716A, a central cannabinoid receptor antagonist, on food-maintained responding*. Pharmacol Biochem Behav 2000, 67(2): 265-70.

22. Di Marzo, V., Goparaju, S.K., Wang, L. et al. *Leptin-regulated endocannabinoids are involved in maintaining food intake*. Nature 2001, 10(6830): 822-5.

23. Blundell, J.E., Jebb, S.A., Stiubbs, R.J. et al. *Effect of rimonabant on energy intake, motivation to eat and body weight with or without hypocaloric diet: The REBA study*. Obesity Rev 2006, 7(Suppl. 2): 104.

24. Liu, Y.L., Connoley, I.P., Wilson, C.A., Stock, M.J. *Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice*. Int J Obesity 2005, 29(2): 183-7.

25. Ravinet Trillou, C., Delgorge, C., Menet, C., Arnone, C., Soubrié, P. *CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity*. Int J Obes Relat Metab Disord 2004, 28(4): 640-8.

26. Christensen, R., Kristensen, P.K., Bartels, E.M., Bliddal, H., Astrup, A. *Efficacy and safety of the weight-loss drug rimonabant: A meta-analysis of randomised trials*. Lancet 2007, 370(9600): 1671-2.

27. Fong, T.M., Guan, X.M., Marsh, D.J. et al. *Antiobesity efficacy of a novel cannabinoid-1 receptor inverse agonist, N-[(1S,2S)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-[[5-(trifluoromethyl)pyridin-2-yl]oxy]propanamide (MK-0364), in rodents*. J Pharmacol Exp Ther 2007, 321(3): 1013-22.

28. Stribling, D.S., Camacho, R.C., Lin, L.S. et al. *In vivo characterization of a novel and selective cannabinoid receptor 1 inverse agonist*. 36th Annu Meet Soc Neurosci (Oct 14-18, Atlanta) 2006, Abst 457.9/CC1.

29. Yu, H., Stribling, D.S., Shearman, L.P. et al. *A novel cannabinoid 1 receptor inverse agonist reduces food intake and body weight in rats – Correlation of pharmacological effect with brain receptor occupancy*. 36th Annu Meet Soc Neurosci (Oct 14-18, Atlanta) 2006, Abst 457.10/CC2.

30. Addy, C., Wright, H., Van Laere, K. et al. *The acyclic CB1R inverse agonist taranabant mediates weight loss by increasing energy expenditure and decreasing caloric intake*. Cell Metab 2008, 7(1): 68-78.

31. De Lepeleire, I., Addy, C., Rothenberg, P. et al. *Brain CB-1 receptor occupancy of taranabant in lean subjects using CB-1R PET*. 43rd Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 17-21, Amsterdam) 2007, Abst 0831.

32. Addy, C., Rothenberg, P., Burns, D. et al. *Clinical evaluation of brain CB-1 receptor occupancy of a novel CB-1R inverse agonist using CB-1R PET*. 67th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 22-26, Chicago) 2007, Abst 2738-PO.

33. Addy, C., Heymsfield, S., Cilissen, C. et al. *Taranabant increases energy expenditure in overweight and moderately obese subjects*. 43rd Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 17-21, Amsterdam) 2007, Abst 0832.

34. Addy, C., Heymsfield, S., Cilissen, C. et al. *MK-0364, a novel cannabinoid-1 receptor inverse agonist, increases energy expenditure in overweight and moderately obese subjects*. 67th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 22-26, Chicago) 2007, Abst 1828-P.

35. Wright, D., Stevens, C., Cilissen, C. et al. *The CB-1R inverse agonist taranabant reduces acute food intake in overweight/obese male volunteers*. 43rd Annu Meet Eur Assoc Study Diabetes (EASD) (Sept 17-21, Amsterdam) 2007, Abst 0833.

36. Stevens, C., Cilissen, C., De Smet, M. et al. *MK-0364, a CB-1R inverse agonist, reduces acute food intake in overweight/obese male volunteers*. 67th Annu Meet Sci Sess Am Diabetes Assoc (ADA) (June 22-26, Chicago) 2007, Abst 1830-P.

37. *A study of MK0364 in obese patients (NCT00131391)*. ClinicalTrials.gov Web site, February 14, 2008.

38. *An eighteen month efficacy and safety study in obese patients (NCT00131430)*. ClinicalTrials.gov Web site, February 14, 2008.

39. *A one year investigational drug study to assess weight loss in patients with type 2 diabetes mellitus (NCT00430742)*. ClinicalTrials.gov Web site, February 14, 2008.

40. *A weight maintenance study in obese patients (NCT00420589)*. ClinicalTrials.gov Web site, February 14, 2008.

41. *An investigational drug study in obese (considerably overweight) patients (NCT00109148)*. ClinicalTrials.gov Web site, February 15, 2008.

42. *A study to investigate a research drug as an aid for smoking cessation in chronic cigarette smokers (NCT00109135)*. ClinicalTrials.gov Web site, February 15, 2008.

43. Schwartz, J.L., Yuan, J., Li, S. et al. *Influence of taranabant, a novel cannabinoid-1 receptor (CB-1R) inverse agonist, on ethinyl estradiol and norelgestromin pharmacokinetics*. 36th Annu Meet Am Coll Clin Pharmacol (ACCP) (Sept 9-11, San Francisco) 2007, Abst 43.