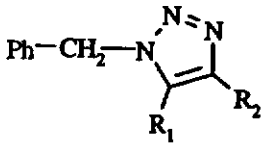
USE OF FLUORINATED TRIAZOLES FOR TREATING PAIN AND AFFECTIVE OR ATTENTION DISORDERS

The present invention relates to new pharmaceutical uses of fluorinated triazoles.

More particularly the present invention relates to new pharmaceutical uses for compounds of formula I



(I)

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by 1 or 2 halogen atoms selected from fluorine and chlorine, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl.

The compounds of formula I as well as their production process are known e.g. from European Patent No. 199 262. This patent also discloses the use of the compounds of formula I for the treatment of convulsions of different origin, e.g. of epilepsy.

In accordance with the present invention, it has now surprisingly been found that the compounds of formula I are useful in the treatment of neuropathic pain, affective disorders including bipolar mood disorders, and attention disorders.

The activity of the compounds of formula I in the treatment of neuropathic pain is evidenced, for example, in the following models of neuropathic pain in the rat and guinea-pig:

Wistar rats or Dunkin Hartley guinea pigs are anaesthetised with enflurane (in N_2O:O_2 for guinea pigs) and the left sciatic nerve is exposed and partially ligated with thread. This procedure produces a mechanical hyperalgesia which develops within 2-3 days and is maintained for at least 4 weeks. Paw withdrawal thresholds to a pressure stimulus are measured using an analgesymeter. Mechanical thresholds are taken on both the ipsilateral (ligated) and contralateral (unligated) paw prior to and then up to 6 hours following drug or

vehicule administration. Reversal of hyperalgesia at each time point is calculated. Groups of 6 animals are used. Statistical analysis is carried out on withdrawal threshold readings using ANOVA followed by Tukey's HSD test.

In the rat model, the compounds of formula I significantly reverse neuropathic mechanical hyperalgesia at doses of about 10 to about 300 mg/kg p.o. With the compound 1-(2,6-difluorophenyl)methyl-1H-1,2,3-triazole-4-carboxamide, for example, a maximal reversal of neuropathic mechanical hyperalgesia of 30% is achieved after 3 hours on administration of 10 mg/kg p.o.

In the guinea pig model, the compounds of formula I significantly reverse neuropathic mechanical hyperalgesia at doses of about 3 to about 100 mg/kg p.o. With the above-mentioned carboxamide, for example, a maximal reversal of neuropathic mechanical hyperalgesia of 60% is achieved after 3 hours on administration of 30 mg/kg p.o.

The activity of the compounds of formula I in the treatment of neuropathic pain can be confirmed in clinical trials, for example in the following study aimed at evaluating the efficacy of a compound in treating chronic pain in patients with diabetic neuropathy:

Patients are randomized to receive 2400 mg/day of the compound or placebo in a 1:1 ratio.

The study consists of a Pre-randomization Phase (1 week) and a Double-blind Phase (5 weeks). The double-blind Phase consists of three periods: a one week Titration Period, a three-week Maintenance Period and a one-week Follow-up Period.

During the 1-week Pre-randomization Phase, the eligibility of the patients is evaluated. Patients meeting all inclusion/exclusion criteria are randomized to either the compound or placebo in the Double-blind Phase. During the 1-week Titration Period, study medication is up-titrated from 800mg/day (given b.i.d.) to 2400 mg/day (given b.i.d.). Patients who complete the 1-week Titration Period then enter the 3-week Maintenance Period. Patients who complete the 3-week Maintenance period or prematurely discontinue double-blind treatment then enter the 1-week Follow-up Period. Study medication is completely withdrawn on entry into the Follow-up Period. During the Double-blind Phase, serial efficacy and safety assessments are obtained.

120 male and female outpatients, aged 18-65 years with a clinical diagnosis of diabetes mellitus (type I or II) and a history of pain associated with diabetic neuropathy for 6 months to 3 years prior to study entry, are randomized 1:1 to the compound or placebo.

The total score of the Short-Form McGill Pain Questionnaire (SF-MPQ) at the end of Maintenence Period is used as primary efficacy parameter. Average weekly pain severity rating (daily patient pain diary) from start of randomized treatment to end of Maintenance Period, usage of rescue medication during the Titration and Maintenance Period, and average pain severity rating during the Follow-up Period (rebound pain), are used as secondary efficacy parameters.

The SF-MPQ total pain score at the end of the Maintenance Period is analyzed using an analysis of covariance model adjusting for the effect of treatment on post-treatment scores by using the baseline SF-MPQ total pain score as a covariate. Average weekly pain severity is analyzed using an analysis of covariance model with repeated measures using the treatment week and the mean pain severity rating during the Pre-randomization Phase as covariates. Usage of rescue medication during the Double-blind Phase is analyzed using the Cochran-Mantel-Haenszel test controlling for center. The mean pain severity rating during the Follow-up Period (rebound pain) is analyzed using an analysis of covariance model adjusting for the effect of treatment on the mean pain severity rating of the Follow-up Period with the mean pain severity rating during the Prerandomization Phase as a covariate.

In this study, the compounds of formula I, more particularly 1-(2,6-difluorophenyl)methyl-1H-1,2,3-triazole-4-carboxamide, are found to decrease pain severity ratings relative to placebo during the Maintenance and Follow-up Periods, in a statistically significant way.

The compounds of formula I are therefore useful in the treatment of neuropathic pain and associated hyperalgesia, including trigeminal and herpetic neuralgia, diabetic neuropathic pain, migraine, causalgia and deafferentation syndromes such as brachial plexus avulsion.

The activity of the compounds of formula I in the treatment of affective and attention disorders treatment is evidenced, for example, in the following tests suitable for detecting drugs having potential behavioural disinhibitory and/or sociotropic effects which are thought to be relevant for recovery from social withdrawal, a cardinal feature of depression and related psychiatric conditions.

a) **The half enclosed platform test**

This test is basically as described in Psychopharmacology, 1986, 89:31-37.

Groups of 12 male OF-1 mice are given vehicle or the substance 1 hour before being tested on the platform. The apparatus consists of a transparent platform perforated with 25 equally-spaced 1 cm holes. The platform is divided into equal halves by a 15 cm high, semi-rectangular wall enclosing one half of the platform, the other half having open edges. The whole platform rests on four 15 cm high legs. A line down the middle runs from the edge of one wall to the edge of the opposite wall. The experiment consists of placing a mouse on the midline and recording their behaviour for 5 minutes as they explore the platform. In particular, the mean frequencies and durations of the behavioural elements are recorded and statistical comparisons are determined using the Kruskal-Wallis "H" test followed by paired comparisons between control and treatment groups using the Mann-Whitney U-test. Probabilities ($p=/<0.05$) quoted are 2-tailed.

At doses of about 0.3 to about 10 mg/kg p.o., the compounds of formula I significantly increase exploratory behaviour, such as stretched attend posture, head raising and forward locomotion, in the open half of the platform, which decreasing the frequency of stationary elements, such as sitting still and inactivity, in the enclosed half of the platform.

b) **The intruder mouse test**

This test is basically as described in Triangle, 1982, 21:95-105 and J. Clin. Psychiatry, 1994, 55:9 (suppl. B) 4-7.

A grouped "intruder" mouse is given the substance or the vehicle route 1 hour before being confronted for 6 minutes with an untreated isolated, aggressive mouse (resident) in a neutral cage. Each group consisted of 8 mice. The social encounter is videotaped and an observer records occurrence and duration of over 60 behavioural elements covering the non-social and social forms of the animals' behavioural repertoire. Frequency, duration and, when required, the sequence of the elements are recorded. The median frequencies and durations of the behavioural elements are recorded for each category and statistical comparisons are determined using the Kruskal-Wallis "H" test followed by paired comparisons between control and treatment groups using the Mann-Whitney "U" test. Probabilities ($p=/<0.05$) quoted are 2-tailed.

At doses of about 1 to about 10 mg/kg p.o., the compounds of formula I significantly increase non-social behaviour and social investigation in the treated intruder mouse, while reducing defensive ambivalence, arrested flight and escape.

In view of their behavioural desinhibitory (= anxiolytic-/antidepressant- like) and sociotropic activity, the compounds of formula I are useful in the treatment of affective disorders including bipolar disorders, e.g. manic-depressive psychoses, extreme psychotic states e.g. mania, schizophrenia, and excessive mood swings where behavioural stabilization is desired. In addition, the compounds are indicated in ADHD (attention deficit hyperactivity disorders) and other attention disorders, e.g. autism, anxiety states, generalized anxiety and agoraphobia, as well as those behavioural states characterized by social withdrawal e.g. negative symptoms.

In a preferred group of formula I for use according to the invention, Ph is o-fluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl or 2-chloro-6-fluorophenyl, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl. The compound 1-(2,6-difluorophenyl)methyl-1H-1,2,3-triazole-4-carboxamide is particularly preferred.

For the above-mentioned indications the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 1 to about 50 mg/kg

animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 50 to about 3500 mg of a compound according to the invention conveniently administered, for example, in divided doses up to four times a day.

The compounds of formula I may be administered in any usual manner, e.g. orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injection solutions or suspensions.

The present invention also provides pharmaceutical compositions comprising a compound of formula I in association with at least one pharmaceutical carrier or diluent, for use in the treatment of neuropathic pain. Such compositions may be manufactured in conventional manner. Unit dosage forms may contain for example from about 10 mg to about 1500 mg of the compound of formula I.

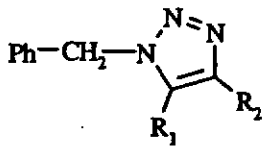
For example tablets each containing 50 mg, or film-coated tablets each containing 100 mg, of 1-(2,6-difluorophenyl)methyl-1H-1,2,3-triazole-4-carboxamide, may be prepared as described in Examples 15 and 16 of EP 199262.

The invention further provides the use of a compound of formula I for the manufacture of a pharmaceutical composition for the treatment of neurophatic pain and affective and attention disorders.

The invention furthermore provides a method for the treatment of neurophatic pain and affective and attention disorders in a subject in need of such treatment, which comprises adrninistering to said subject a therapeutically effective amount of a compound of formula I.

Claims:

1. The use of a compound of formula I



(I)

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by 1 or 2 halogen atoms selected from fluorine and chlorine, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, for the manufacture of a pharmaceutical composition for the treatment of neurophatic pain and affective and attention disorders.