Pharmacological Characterization of the Novel Anxiolytic β-Carbol ine Abecarnil in Rodents and Primates

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ABSTRACT—β-Carbol ine abecarnil was behaviorally and biochemically characterized as a new anxiolytic agent in rodents and primates in comparison with the benzodiazepine (BZ) anxiolytics. Oral treatment with abecarnil (0.5–10 mg/kg) showed a potent anticonflict activity in the water-lick test in rats. The minimal effective dose was lower than those of BZ anxiolytics, such as etizolam, diazepam, clotiazepam and tofisopam. Abecarnil also showed taming effects to suppress fighting and aggressive behaviors in mice and monkeys with little sedative and ataxic effects, in contrast to the BZ anxiolytics producing marked sedative and ataxic effects. Furthermore, abecarnil suppressed both the sedative and ataxic effects induced by diazepam. Abecarnil bound to rat cerebellar BZ1 receptors (Kᵢ=0.24 nM) with a higher affinity than to rat spinal cord BZ2 receptors (Kᵢ=1.3 nM), whereas BZ derivatives bound to both the receptors with a low and equal affinity. GABA-ratios of abecarnil were 1.9 for the BZ₁ receptors and 2.8 for the BZ₂ receptors, and they were smaller than those of diazepam and flunitrazepam. Thus, in contrast to the BZ derivatives, abecarnil may act as a selective partial agonist at central BZ₁ receptors, resulting in its potent anticonflict and taming effects with little sedative and ataxic effects.

Keywords: Abecarnil, Anxiolytic, β-Carbol ine, Benzodiazepines, GABA

Benzodiazepines (BZs) as effective anxiolytics have been the most widely used drugs in the treatment of anxiety disorders. However, BZs have been reported to show unwanted side effects such as sedation, ataxia and amnesia. The development of tolerance and dependence also have arisen as unwanted features in the long-term use of BZs as anxiolytics. For these reasons, the drug development in this field recently has been directed to the search for a new anxiolytic without unwanted side effects.

Abecarnil (ZK 112119; isopropyl 6-benzyloxy-4-methoxymethyl-β-carbol ine-3-carboxylate, Fig. 1) has been developed as a new anxiolytic with an advantageous pharmacological profile over BZs (1). Previous biochemical and pharmacological studies have indicated that abecarnil acts as a partial agonist at central BZ receptors with a high binding affinity and exerts marked anxiolytic and anticonvulsant actions, but in contrast to diazepam, only weak or no sedative and ataxic effects (1–4). In addition, there was no development of tolerance to the anticonvulsant effects of abecarnil in dogs in contrast to BZs (5).

On the other hand, there are known to be at least three types of BZ receptors, BZ₁ (type-I), BZ₂ (type-II) and BZₚ (peripheral type) in mouse, rat, monkey and human brain (6–9). BZ₁ and BZ₂ receptors, which are termed central BZ receptors, are associated with the GABAₐ/BZ receptor complex and modulate the GABA neuronal function.

Fig. 1. Chemical structure of abecarnil.
The BZ₁ and BZ₂ receptors coexist in the cerebral cortex and hippocampus, but the former is rich in the cerebellum, and the latter is rich in the spinal cord (10, 11). The BZ₃ receptor is abundant in glia cells and many peripheral tissues such as the kidney and lung (8). These subtypes seem to play different functional roles in the brain, but so far their function have not been clarified sufficiently yet.

One purpose of the present study is to characterize the pharmacological activities of abecarnil. Thus the anxiolytic, sedative and ataxic effects of abecarnil in rodents and primates were examined in comparison with those of anxiolytic BZs. The second purpose of the present study is to clarify the interactions of abecarnil with BZ-receptor subtypes. Thus, interactions of abecarnil with rat cerebellar, spinal cord and kidney BZ receptors were examined in comparison with those of drugs acting at BZ receptors. On the basis of the data on these behavioral and BZ-receptor binding studies, we discuss the mechanism underlying the specific pharmacological activities of the novel anxiolytic abecarnil.

MATERIALS AND METHODS

Drugs

Abecarnil, ZK 93426 (ethyl 5-isopropoxy-4-methyl-β-carboline-3-carboxylate) (Scherer AG, Berlin, FRG); diazepam, flumazenil, flunitrazepam (Hoffmann-La Roche, Basel, Switzerland); β-CCE (ethyl β-carboline-3-carboxylate: Research Biochemical, Inc., Wayland, MA, USA); GABA (Wako Chemicals, Osaka); bicuculline (Sigma Chemical Co., St. Louis, MO, USA); etizolam (Rize®), cliotiazepam (Depas®) (Yoshitomi Pharmaceutical Industries, Ltd., Osaka); tofisopam (Grandaxin®: Mochida Pharmaceutical Co., Ltd., Tokyo) and hexobarbital (Bayer, Leverkusen, FRG) were from the suppliers indicated in parentheses. For the rodents, the test drugs were suspended in a solution containing 0.5% carboxymethylcellulose-Na/0.04% Tween 80 (W/W) and administered orally 60 min prior to the test with an injection volume of 10 ml/kg unless otherwise indicated. For the monkeys, drugs were suspended into physiological saline containing 5% Cremophor EL (Sigma Chemical Co.) and administered intraperitoneally with an injection volume of 1 ml/kg.

Water-lick conflict test in rats

This test was carried out according to the method of Hjorth et al. (12) with the following modifications. After water-deprivation overnight (18 hr), male Wistar rats (Clea Japan, Inc., Osaka) were allowed to drink 5.5 (W/V)% glucose solution through the spout of the drinking bottle for 5 min in the test chamber. Then they had a 45-min free-drinking session in their home cage. Animals that had drunk for more than 3 min at the spout in the test chamber were selected for tests and subjected to water-deprivation overnight (18 hr). On the test day, the animals were allowed to drink the glucose solution through the spout in the test chamber. After consecutive drinking for 10 sec, every subsequent drinking attempt was punished with an electric shock applied between the spout and the grid floor (2 mA direct current, delivered for 100 msec every 3 sec). The number of shocks received during a 5-min test session was recorded.

Effects on foot-shock induced fighting behavior in mice

Prior to the test, male ICR mice (Clea Japan, Inc.) weighing 18 to 30 g were fasted for 18 hr, with free access to tap water. According to the method of Tedeschi et al. (13), a pair of mice were confined in an acrylic case (13 x 13 x 16 cm) with a steel grid floor and subjected to electric shocks (5 HZ, 2 msec, 6 mA). Each succession of fighting behavior, in which both mice stand on their hind legs, spar and bite at each other, was counted as one fighting episode. Only those pairs that exhibited more than 5 fighting episodes within 3 min in the control schedule were selected for the test schedule. In the test schedule, 60 min after oral administration of drugs, the fighting behavior was counted for 3 min. For the calculation of the ED₅₀ value, the number of pairs exhibiting less than 6 fighting episodes was determined.

Hexobarbital-induced loss of the righting reflex in mice (hexobarbital sleep test)

Prior to the test, male ddY mice (Clea Japan, Inc.) weighing 19 to 29 g were fasted for 18 hr, with free access to tap water. Each animal was placed gently on its back on a hot plate (32±2°C) after intraperitoneal injection of hexobarbital (70 mg/kg) with an injection volume of 10 ml/kg. The duration of loss of the righting reflex was measured in each animal.

Traction test in mice

The traction test was carried out immediately before hexobarbital injection in the tests described above. Each animal was suspended through its fore paws to a metallic wire (2-mm diameter) stretched horizontally at a height of 25 cm. The incidence of ataxia was defined as the percentage of animals that failed to grasp the wire with a hind paw within 10 sec.

Behavioral effects in cynomolgus monkeys

Four male cynomolgus monkeys (Macaca fascicularis: Clea Japan, Inc.), weighing 4 to 7 kg, were housed individually in the standard animal quarters on a 12-hr light-dark cycle. Their diet consisted of standard monkey chow and fresh fruit. Behavioral changes in animals were scored by the method of Wada et al. (14) with some
modifications, using a rating scale of 0–2 (0: none, 1: moderate, 2: severe) on the behaviors listed in Table 1. The summed score including excitement, belligerence and defensiveness was defined as an aggression score. The behavioral assessment was carried out up to 4.5 hr after drug administration by an examiner who was unaware of the treatment conditions. Animals were subjected to the drug treatment at 2:00 PM at a one week interval.

**Table 1.** A list of behaviors in cynomolgus monkeys to assess behavioral effects of abecarnil and diazepam

| Symptoms          | Behaviors                              |
|-------------------|----------------------------------------|
| Belligerence      | angry bark, head lowering, lunging forward, swatting |
| Excitement        | chattering, mouthing, jumping around   |
| Defensiveness     | withdrawing, baring teeth, opening mouth |
| Ataxia/Sedation   | postural instability, drowsiness        |

BZ binding studies

Male Wistar rats (Clea Japan, Inc.), weighing 200 to 300 g, were decapitated; and their cerebellum, spinal cord and kidney were dissected. The cerebellum and spinal cord were homogenized at 0–4°C in 20 vol. of 50 mM Tris-citrate buffer (pH 7.1), centrifuged for 15 min at 40,000×g and washed 3 times. The pellets were frozen and stored at −30°C for more than 18 hr and resuspended in 50 mM Tris-HCl buffer (120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, pH 7.4) for the binding assay. According to the method of Schoemaker et al. (8), the kidney was homogenized at 0–4°C in 50 vol. of phosphate-buffered saline (181 mM Na⁺, 9.5 mM K⁺, 50 mM PO₄⁻³, pH 7.5) and filtered through 4 layers of sterile gauze.

Cerebellar and spinal cord membrane suspension (0.5 mg protein/tube) was incubated at 37°C for 30 min with [³H]flumazenil (New England Nuclear, Boston, MA, USA: 83 Ci/mmol) and various concentrations of test drugs in the presence of 100 μM GABA or 100 μM bicuculline in a final vol. of 2.5 ml. Test drugs were dissolved in dimethylsulfoxide (DMSO), and thus the final concentration of DMSO in the assay system was 0.4% throughout. Then the sample was filtered under vacuum through Whatman GF/B filters followed by three washes, each with 10 ml of the ice-cold buffer. The non-specific binding was defined in the presence of 10 μM flunitrazepam. The Kᵦ values of [³H]flumazenil for the cerebellar and spinal cord membranes were 8.8 nM and 7.1 nM, respectively. Kidney membrane suspension (0.2 mg protein/tube) was incubated at 37°C for 120 min with [³H]Ro 5-4864 (New England Nuclear: 81.3 Ci/mmol) and various concentrations of test drugs in a final volume of 2.5 ml. Then the sample was filtered under vacuum through Whatman GF/B filters followed by three washes, each with 5 ml of the ice-cold buffer. The non-specific binding was defined in the presence of 100 μM diazepam. The Kᵦ value of [³H]Ro 5-4864 was 18 nM. The amounts of protein were determined by the method of Lowry et al. (15).

Fig. 2. Effects of abecarnil, etizolam, diazepam, clotiazepam and tofisopam in the water-lick conflict test in rats. Each value represents the mean±S.E. of 8–18 rats. *: P<0.05, **: P<0.01, compared with the control (Dunnett’s test).
Statistical analyses

Data were expressed as the mean ± S.E. Values were considered significant when the P value was less than 0.05 by Dunnett's test, Fisher's exact probability test, the Mann-Whitney U-test or the unpaired t-test as appropriate. The ED50 value (95% confidence limits) was calculated by the log-probit method.

RESULTS

Effects in the water-lick conflict test of rats

Anticonflict effects of abecarnil and BZs in rats are shown in Fig. 2. Abecarnil (0.5 – 10 mg/kg) induced a significant increase in the number of shocks received 1 hr after oral administration, and the maximal effect was obtained at a dose of 5 mg/kg. Etizolam (20 mg/kg), diazepam (20 – 50 mg/kg), clotiazepam (50 mg/kg) and tofisopam (300 mg/kg) also induced a significant increase in the number of shocks. The minimal effective dose of abecarnil was found to be 0.5 mg/kg, p.o., and it was the lowest among those of the drugs tested.

Effects on foot-shock induced fighting behaviors in mice

Both abecarnil and diazepam elicited a significant decrease in the number of the foot-shock induced fighting episodes in a dose-dependent manner (Fig. 3). The ED50 values of abecarnil and diazepam were 2.0 (0.8 – 9.0) and 0.7 (0.3 – 1.3) mg/kg, p.o., respectively.

Effects on hexobarbital-induced loss of the righting reflex in mice

Abecarnil (10 – 100 mg/kg, p.o.) slightly prolonged the duration of the hexobarbital-induced loss of the righting reflex, but the effect was not dose-dependent (Fig. 4). On the other hand, BZs tested elicited marked and dose-dependent potentiation of the loss of righting reflex (Fig. 4). The minimal effective dose of abecarnil (10 mg/kg, p.o.) was higher than those of etizolam (1 mg/kg, p.o.), diazepam (3.2 mg/kg, p.o.) and clotiazepam (1 mg/kg, p.o.).

Abecarnil (0.1 – 1.0 mg/kg, i.p.) alone did not affect the hexobarbital-induced loss of the righting reflex (Fig. 4).
5). In combination with diazepam (3.2 mg/kg, p.o.), abecarnil (0.32–1.0 mg/kg, i.p.) significantly suppressed the diazepam-induced potentiation of the loss of the righting reflex (Fig. 5).

**Effects in the traction test in mice**

Abecarnil did not induce any impairment of the motor performance of mice in the traction test up to 100 mg/kg, p.o. (Fig. 6). On the other hand, the tested BZs impaired the motor performance, giving rise to the ED50 value of 20 mg/kg, p.o. for etizolam, 9.1 mg/kg, p.o. for diazepam and 8.4 mg/kg, p.o. for clotiazepam. Tofisopam impaired the motor performance in four of ten animals tested at 320 mg/kg, p.o. In combination with diazepam (10 mg/kg, p.o.), abecarnil (32 mg/kg, p.o.) significantly suppressed the impairment induced by diazepam (Fig. 7).

**Effects on aggressive behaviors in cynomolgus monkeys**

Both abecarnil and diazepam (3, 10 mg/kg, i.p.) suppressed aggressive behaviors including belligerence, excitement and defensiveness in a dose-dependent manner in
cynomolgus monkeys (Fig. 8). The effects of both drugs at 10 mg/kg, i.p. were observed at 30 min after the administration and lasted for more than 4 hr. Abecarnil did not show any postural instability in animals at the tested doses (Table 2). Diazepam induced the marked postural instability in animals at the tested doses (Table 2). Abecarnil as well as diazepam induced drowsiness in animals at the tested doses, but it was not statistically significant (Table 2).

| Treatment (mg/kg, i.p.) | Postural Instability | Sedation (hr) |
|-------------------------|----------------------|--------------|
|                         | 0−2                  | 2−4.5        | 0−2 | 2−4.5 |
| Vehicle                 | 0                    | 0            | 0   | 0     |
| Abecarnil 3             | 0                    | 0.8±0.5      | 1.5±1.2 |
| Abecarnil 10            | 0                    | 1.0±0.7      | 2.0±1.2 |
| Diazepam 3              | 0.8±0.8              | 1.0±1.0      | 1.3±1.3 |
| Diazepam 10             | 2.0±0.9*             | 2.3±1.3      | 2.3±0.8 | 1.5±1.2 |

Postural instability and drowsiness were scored on a rating scale of 0−2 (0: none, 1: moderate, 2: severe). The scores were summed at five time points through 0- to 2-hr and 2- to 4.5-hr periods after drug or vehicle-treatment. The value represents a mean score ± S.E. of four animals. *P<0.05 vs. vehicle-treatment as a control (Kruskal-Wallis analysis followed by Mann-Whitney U-test).

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Abecarnil, Anxiolytic β-carbolines

Fig. 9. Displacement by abecarnil and diazepam of [3H]flumazenil bindings to rat cerebellar and spinal cord membranes. Abecarnil, cerebellum (○), spinal cord (○); Diazepam, cerebellum (△), spinal cord (△). Each point represents the mean of three independent determinations.

Fig. 10. Displacement by abecarnil and diazepam of [3H]flumazenil bindings to rat cerebellar membranes in the presence or absence of GABA. Abecarnil in the presence (□) or absence (○) of 100 μM GABA; Diazepam in the presence (△) or absence (△) of 100 μM GABA. Each point represents the mean of three independent determinations.

Table 3. Displacements of [3H]flumazenil bindings from rat cerebellar and spinal cord membranes and of [3H]Ro 5-4864 binding from rat kidney membranes by BZs and β-carbolines

| Drug       | K_i (nM) | K_i ratio |
|------------|----------|-----------|
|            | Cerebellum | Spinal cord | Kidney |
| Flumazenil | 7.6       | 6.3        | >10000 |
| Flunitrazepam | 29       | 30         | 140    |
| Diazepam   | 111       | 126        | 360    |
| ZK 93426   | 0.35      | 1.1        | 2000   |
| β-CCE      | 2.6       | 13         | >10000 |
| Abecarnil  | 0.24      | 1.3        | 1200   |

Cerebellar membranes with 0.3 nM [3H]flumazenil and spinal cord membranes with 1 nM [3H]flumazenil were incubated for 30 min at 37°C in the presence of 100 μM bicuculline. Kidney membranes with 1 nM [3H]Ro 5-4864 were incubated for 120 min at 37°C. Each value is the mean of three independent determinations. K_i ratio: (K_i value in the cerebellum): (K_i value in the spinal cord): (K_i value in the kidney).

Table 4. GABA-ratios of BZs and β-carbolines for the displacement of [3H]flumazenil bindings from rat cerebellar and spinal cord membranes

| Drug       | GABA-ratio |
|------------|------------|
|            | Cerebellum | Spinal cord |
| Diazepam   | 3.25±0.10^a | 4.36±0.40^b |
| Flunitrazepam | 2.63±0.22^a | 5.05±0.76^a |
| Abecarnil  | 1.89±0.20^a | 2.84±0.35^a |
| Flumazenil | 1.23±0.06^a | 1.18±0.08^a |
| ZK 93426   | 0.98±0.20^a | 1.02±0.03^a |
| β-CCE      | 0.57±0.09^a | 0.62±0.10^a |

GABA-ratio: (IC_{50} in the presence of 100 μM bicuculline)/(IC_{50} in the presence of 100 μM GABA). Each value is the mean±S.D. of three or four independent determinations. ^a: P<0.05 vs. diazepam, ^b: P<0.05 vs. flumazenil (Unpaired t-test).

BZ receptors binding

Abecarnil displaced [3H]flumazenil binding to rat cerebellar and spinal cord membranes with much a higher affinity than diazepam (Fig. 9). [3H]Flumazenil binding to the cerebellar membranes was displaced by lower concentrations of abecarnil than those required to displace [3H]flumazenil binding to spinal cord membranes. (Fig. 9). On the other hand, the displacement curves of diazepam in the cerebellar and spinal cord [3H]flumazenil bindings were almost the same (Fig. 9). As shown in Table 3, the K_i values for flumazenil, flunitrazepam and diazepam were almost the same in the cerebellum and spinal cord. On the other hand, the K_i values for abecarnil and β-CCE in the cerebellum were five times lower than those in the spinal cord. Abecarnil, like β-CCE and ZK 93426, displaced [3H]Ro 5-4864 binding to rat kidney membranes with a lower affinity than diazepam and flunitrazepam (Table 3).

Whereas the affinity of diazepam for [3H]flumazenil binding sites in rat cerebellum was markedly enhanced in the presence of 100 μM GABA, the affinities of abecarnil for these receptors was slightly enhanced in the same condition (Fig. 10). The GABA ratios of BZs and β-carbolines in the cerebellum and spinal cord are summarized in Table 4. The GABA ratios of abecarnil were 1.9 in the cerebellum and 2.8 in the spinal cord, and they were smaller than those of diazepam and flunitrazepam, but higher than those of the BZ antagonists, flumazenil and ZK 93426.
DISCUSSION

It has been reported that intraperitoneal administration of abecarnil shows potent anxiolytic activities in rodent models (1). In the present study, oral administration of abecarnil (0.5–10 mg/kg) caused a significant increase in the number of shocks in the water-lick conflict test with rats. The minimal effective dose was found to be lower than that of anxiolytic BZs such as etizolam, diazepam, clotiazepam and tofisopam. Abecarnil, like diazepam, showed taming effects to suppress fighting and aggressive behaviors in mice and monkeys. These results again indicate that abecarnil may exhibit a potent anxiolytic activity clinically.

Despite its potent anxiolytic activity, abecarnil induced only slight effects in tests of sedation and ataxia. The efficacy of abecarnil on potentiating hexobarbital-induced loss of the righting reflex in mice was much weaker than that of the tested BZs. In the traction test, abecarnil failed to impair the motor performance of mice up to 100 mg/kg, p.o., whereas the tested BZs induced the marked impairment. Furthermore, abecarnil antagonized diazepam-induced sedative and ataxic effects in these tests. Also in rodents, abecarnil (3, 10 mg/kg, i.p.) suppressed aggressive behaviors without induction of drowsiness and postural instability, whereas diazepam (3, 10 mg/kg, i.p.) induced postural instability associated with the suppressive effects. Taken together with the behavioral studies in rodents and primates, abecarnil was found to show anxiolytic activity in rodents and primates at doses eliciting little sedative and ataxic effects in contrast to diazepam which shows both effects.

As is common with £-carbolines, abecarnil had a very high affinity for central BZ receptors but a low affinity for peripheral BZ receptors, suggesting that it exhibits its pharmacological action through central BZ receptors. Abecarnil displaced [3H]flumazenil binding from rat cerebellar BZ receptors (K_i=0.24 nM) with about five times higher affinity than that from spinal cord BZ receptors (K_i=1.3 nM), which was in contrast to BZs such as flunitrazepam and diazepam, which show low affinity and no selectivity for these receptors. In the previous studies (8, 9), it has been shown that the BZ receptors in the cerebellum and spinal cord are predominantly of the BZ_1 and the BZ_2-receptor subtypes, respectively. In our study, it was ascertained that zolpidem (data not shown) and 1,5-CCE, BZ-selective ligands (6, 10), had about five times higher affinities for the BZ receptors in the cerebellum than those in the spinal cord. The physiological roles of the BZ_1 and BZ_2 receptors in brain function are not yet clarified, but the sedative and ataxic effects by BZs have been proposed to be due to the over activation of the BZ_1 and BZ_2 receptors, respectively (16–18). Findings that abecarnil had no ataxic effects may be partly due to its lower affinity for spinal cord BZ_2 receptors, but it does not explain the antagonism of diazepam-induced ataxia.

Binding of central BZ-receptor ligands is influenced by the presence of a GABA agonist (17, 19, 20). Thus, the binding of BZ agonists is potentiated in the presence of muscimol or GABA, while the opposite is true for the inverse agonists showing anxiogenic and proconvulsive effects. The binding of BZ antagonists remains unchanged irrespective of the presence of GABA. Therefore, the GABA ratio can be used as an index showing the intrinsic activity of BZ-receptor ligands at the GABA_A/BZ receptor complex (17, 19, 20). In the present study, the GABA ratios of abecarnil at cerebellar and spinal cord BZ receptors were fell between those of the agonists (diazepam and flunitrazepam) and the antagonists (flumazenil and ZK 93426). Thus, abecarnil may be interpreted as a partial agonist at both the BZ_1 and BZ_2 receptors (at least at the receptors in the cerebellum and spinal cord). A partial agonist for the BZ receptors has been reported to be able to block some of the effects elicited by the full agonist (21). The findings that abecarnil showed only weak sedative effects and inhibited the effects induced by diazepam may be consistent with its BZ_1 partial agonist characterization. The partial agonistic action of abecarnil at spinal cord BZ_1 receptors may be supported by the antagonism of diazepam-induced ataxia, which seemed to result from displacing of diazepam from the receptors.

Recently, possible molecular substrates for the BZ-receptor heterogeneity have been provided by the cloning of cDNAs encoding multiple isoforms of £, £ , and Y subunits that are thought to constitute the GABA_A-receptor complex (22). In the different £-isoform coexpressed with £ ( ) and £ ( ) in mammalian cells, the receptors containing the £-subunit displayed the properties of BZ_1 receptors whilst the receptors containing £ or £ or £ subunits displayed the properties of BZ_2 receptors (23, 24). Thus, our present studies suggest that abecarnil may be a selective ligand for the GABA_A receptor containing the £-subunit, which is consistent with the preliminary evidence on reconstituted GABA_A receptors in frog oocytes (25). As to the intrinsic activity, the GABA ratio is likely to represent the average intrinsic activity for a given substance at a variety of GABA_A/BZ receptors. Thus, our present findings suggest that abecarnil may be a partial agonist at GABA_A/BZ receptors containing the £-subunit, and the average intrinsic activity of abecarnil at a mixture of GABA_A/BZ receptors containing £ or £ or £ subunits may be weaker than that of conventional BZs.

In conclusion, in contrast to the BZ derivatives, abecarnil may act as a selective partial agonist at central BZ_1 receptors, resulting in its potent anxiolytic and taming actions.
effects with little sedative and ataxic effects. Thus, Abecarnil might offer a new therapeutic approach for the treatment of anxiety with less side effects in place of conventional BZ anxiolytics.

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