ELSEVIER

Pharmacology, Biochemistry and Behavior 67 (2000) 483–487

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

Effects of benzodiazepine receptor ligands and ethanol in rats trained to discriminate pregnanolone

Kimberly E. Vanover*

CoCensys, Irvine, CA 92618, USA

Received 10 March 2000; received in revised form 10 July 2000; accepted 17 July 2000

Abstract

Although $GABA_A$ receptor positive modulators share many behavioral effects, subtle differences have been detected among their discriminative stimulus effects. The purpose of the present study was to determine the extent of shared discriminative stimulus effects of pregnanolone with various benzodiazepine receptor ligands and with ethanol. Naive male Sprague–Dawley rats were trained to discriminate the endogenous neuroactive steroid pregnanolone (5.6 or 8.0 mg/kg) from vehicle. The benzodiazepine receptor agonists, triazolam and lorazepam, the benzodiazepine receptor partial agonist, bretazenil, the benzodiazepine1 (BZ1) receptor subtype selective agonists, zolpidem and zaleplon and ethanol were tested. Triazolam, lorazepam and bretazenil substituted for pregnanolone. Lorazepam, but not triazolam or bretazenil, decreased response rates at the highest dose tested. Zaleplon completely substituted for pregnanolone with no effect on response rates. Zolpidem substituted for pregnanolone only at a dose that severely disrupted response rates. Ethanol partially substituted for pregnanolone and decreased response rates. The results are consistent with $GABA_A$ receptor mediation of the discriminative stimulus effects of pregnanolone. The effects on response rates suggest subtle differentiation among the $GABA_A$ receptor-mediated cues.

Keywords: Pregnanolone; Neurosteroid; Neuroactive steroid; Drug discrimination; Discriminative stimulus; Behavior; Benzodiazepine; Ethanol

1. Introduction

It has been demonstrated previously that the endogenous neuroactive steroid pregnanolone can function as a discriminative stimulus [23]. Positive modulation of $GABA_A$ receptors is thought to mediate the discriminative stimulus effects of pregnanolone. Further, neuroactive steroids have been shown to share discriminative stimulus effects with other positive modulators of the $GABA_A$ receptor complex [2,10,12,23]. For example, in rats trained to discriminate diazepam or pentobarbital from its vehicle, the neuroactive steroids 3α,21-dihydroxy-5α-pregnan-20-one (3α,5α-THDOC; allotetrahydrodeoxycorticosterone) and 3α-hydroxy-5α-pregnan-20-one (3α,5α-P; allopregnanolone) exhibited full substitution for the training drug [2]. Similarly, pentobarbital generalized to 3α,21-dihydroxy-3β-trifluoromethyl-5β-pregnan-20-one (Co 8-7071), a synthetic neuroactive steroid in monkeys trained to discriminate pentobarbital from saline [15]. Additionally, allopregnanolone substituted for ethanol in monkeys [12]; allotetrahydrodeoxycorticosterone and 3α,21-dihydroxy-5β-pregnan-20-one (3α,5β-THDOC; tetrahydrodeoxycorticosterone) have been shown to substitute for ethanol in rats [1,8].

However, subtle differences among the discriminative stimuli of various $GABA_A$ receptor positive modulators are well documented. For example, the benzodiazepine diazepam and the barbiturate pentobarbital exhibit cross-generalization and diazepam and another benzodiazepine lorazepam exhibit cross-generalization, but pentobarbital and lorazepam exhibit asymmetrical cross-generalization with pentobarbital generalizing to lorazepam and lorazepam failing to generalize to pentobarbital [4]. Thus, although there appears to be some crossover, the discriminative stimulus effects of benzodiazepines and barbiturates are not identical. Differences among the discriminative stimulus effects of benzodiazepine ligands have been reported as well. Bretazenil, a partial agonist at benzodiazepine receptors, completely substitutes for the full benzo-

* ACADIA Pharmaceuticals, 3911 Sorrento Valley Boulevard, San Diego, CA 92121-1402, USA. Tel.: +1-858-320-8633; fax: +1-858-558-2872.

E-mail address: kvanover@acadia-pharm.com (K.E. Vanover).

0091-3057/00/$ – see front matter
PII: S0091-3057(00)00394-4

diazepine agonist chlordiazepoxide as a discriminative stimulus, whereas bretazenil attenuates the discriminative stimulus effects of the benzodiazepine1 (BZ1) receptor subtype selective agonist zolpidem [16]. Further differences among $GABA_A$ receptor positive modulators have been revealed using three-choice procedures. For example, humans were able to acquire a discrimination between zolpidem and the nonselective benzodiazepine agonist triazolam in a three-choice procedure (zolpidem vs. triazolam vs. placebo; [14]).

The purpose of the present experiment was to determine the extent similarities and differences among the discriminative stimulus effects of pregnanolone compared to various benzodiazepine receptor ligands and to ethanol. The nonselective benzodiazepine full agonists, triazolam and lorazepam and the benzodiazepine partial agonist bretazenil were tested. In addition, the BZ1 receptor subtype selective full agonists zolpidem and zaleplon were evaluated.

2. Method

The "Guide for the Care and Use of Laboratory Animals" was followed in our Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) - accredited facilities for all experiments.

2.1. Animals

Naive male rats (Sprague–Dawley, Harlan Sprague–Dawley; San Diego, CA) weighing approximately 280 g were individually housed in polycarbonate cages containing sterilized bedding material (Sani-Chips, P.J. Murray; Montville, NJ) in a room maintained at 23.0°C (±2.5°C) and on a 12:12 h light:dark cycle. Food (Teklad LM 485, Harlan Teklad; Placentia, CA) was restricted to post-session supplements (approximately 10 g per day) sufficient to maintain stable body weights (±5%) and behavioral performance. Sessions were conducted generally 5 days per week and rats were fed 10–15 g food per day on days with no session (i.e., weekends and holidays). Water was freely available in the home cage.

2.2. Apparatus and procedure

For experimental sessions, rats were placed in sound-attenuating chambers (30 × 24 × 33 cm; Coulbourn Instruments; Lehigh Valley, PA) equipped with two response levers with associated stimulus lights. A magazine for the sucrose dipper and its associated light were located between the two levers. Med-Associates (East Fairfield, VT) computer software and interface controlled stimulus events and recorded lever presses.

The procedure is similar to that previously reported [23]. Initially, rats ($n=10$) were trained to discriminate 5.6 mg/kg pregnanolone from vehicle (50:50 hydroxypropyl-β-cyclodextrin:0.9% saline) in a two-lever, sucrose-reinforced (110 g sucrose/1 l water) drug discrimination paradigm. In order to increase discriminative control, those rats ($n=6$) that could tolerate a higher dose (i.e., a higher dose did not significantly reduce response rate) were switched to 8.0 mg/kg pregnanolone as the training stimulus about halfway through the study (in some animals before substitution tests began and in others after some of the substitution tests had occurred). The training dose did not appear to influence the efficacy of the test drugs. Experimental sessions lasted 20 min or until 50 reinforcers were earned. Rats were injected with either saline (1.0 ml/kg ip) or pregnanolone (5.6 or 8.0 mg/kg, ip). Fifteen minutes following injection, rats were placed in the operant chambers and the session began with stimulus lights lit above both levers. The pre-session injection determined the appropriate response lever. A vehicle injection indicated that 10 consecutive presses (fixed ratio 10; FR 10) on the right lever would be reinforced with sucrose availability, whereas an injection of pregnanolone indicated that 10 consecutive presses on the left lever would be reinforced. It should be noted that the position of the levers were not counterbalanced for drug vs. vehicle conditions, which may have resulted in a potential confound of lever preference; however, previous studies that have counterbalanced the position of the levers have made no mention of differential lever preference [2,18].

Sucrose availability (0.1 ml) occurred for 4 s during which time the stimulus lights were turned off and responding had no consequence. Responses on the inappropriate lever during the course of the session reset the response requirement on the appropriate lever. In addition, 10 consecutive presses on the inappropriate lever resulted in a 10-s time-out in which stimulus lights were turned off and responding had no consequence. Pregnanolone (P) and vehicle (V) were administered in a fixed daily sequence (SVVSSVSSVV). Training was continued until rats reached a testing criterion of at least 80% injection-appropriate responses before the first reinforcer and at least 90% injection-appropriate responses over the entire session for at least seven of eight consecutive sessions.

After acquisition of the discrimination, test sessions (T) were conducted according to the daily sequence (VTP-VTPTVPT) as long as performance in the intervening training sessions remained at or above the testing criterion level. If performance of a rat failed to reach criterion, then the rat would return to the fixed daily sequence without testing until testing criterion again was achieved. Test sessions were identical to training sessions except that a test drug or its vehicle was administered and both levers were active such that 10 consecutive responses on either lever produced sucrose. Again, experimental sessions lasted 20 min or until 50 reinforcers were earned. A dose–response function for pregnanolone was determined first with doses administered in a pseudo-random order, followed by substitution tests. Drugs were tested with a subgroup of five rats, randomly chosen, except the training drug, which

was tested with nine rats. The 10th rat was sacrificed due to poor health unrelated to the study about halfway through the experiment; the data from this rat were not included. A complete dose–response function of each drug was completed before testing with the next drug was started and drug order for each rat varied. Each dose was tested only once. Test drugs were injected intraperitoneally and included pregnanolone (1.0–10.0 mg/kg, 15-min pretreatment interval), bretazenil (0.1–3.0 mg/kg, 30 min), triazolam (0.003–0.3 mg/kg, 30 min), lorazepam (0.1–3.0 mg/kg, 30 min), zolpidem (0.3–3.0 mg/kg, 30 min), zaleplon (0.3–3.0 mg/kg, 30 min) and ethanol (0.5–1.25 g/kg, 30 min).

2.3. Data analysis

The means and standard errors of the percentage of total responses occurring on the pregnanolone-appropriate lever during test sessions were calculated. If a rat failed to earn at least one reinforcer in any test session, the data from that session were not included in the calculation for pregnanolone-appropriate responses, but were included for the rate of responding measure. A test drug was considered to have substituted for the discriminative stimulus effects of pregnanolone if it engendered at least 80% pregnanolone-appropriate responding over the entire session. Substitution between 20% and 80% pregnanolone-appropriate responding was designated as partial substitution. Less than 20% pregnanolone-appropriate responding indicated no substitution. Data are described in terms of full, partial or no substitution based on average data and based on the number of individual animals exhibiting substitution at any given dose. The number of individual rats exhibiting substitution vs. the number rats responding at any given dose are shown in the figures.

The rate of responding on both levers during test sessions was calculated as responses per second for each rat. Means and standard errors were calculated and shown.

2.4. Drugs

A vehicle of 50:50 hydroxypropyl-β-cyclodextrin:0.9% saline was used to dissolve pregnanolone synthesized by AKZO-Diosynth (Oss, The Netherlands), triazolam (Research Biochemicals International, RBI, Natick, MA), lorazepam (Sigma, St. Louis, MO) and zolpidem (RBI). Bretazenil (generously supplied by Dr. J.M. Witkin at the National Institute on Drug Abuse, National Institute of Health) and zaleplon (generously supplied by Drs. S. Rosenzweig-Lipson and J.E. Barrett at Wyeth-Ayerst, Princeton, NJ) were suspended in 10% Tween 80 (90% deionized water). Ethanol (Spectrum; Gardena, CA) was diluted with 0.9% saline for the appropriate concentrations. All drugs were administered intraperitoneally in a volume of 1.0 ml/kg. Pregnanolone and zolpidem were administered 15 min before the session, whereas all other compounds were administered 30 min before the session.

3. Results

The neuroactive steroid pregnanolone at 5.6 mg/kg was trained as a discriminative stimulus in nine rats. All of the rats reached criteria to test. The mean number of sessions required for training to test criteria was 73.5 sessions (range = 41–111). Due to poor stimulus control, six rats were switched to a training dose of 8.0 mg/kg approximately halfway through the study. Stimulus control was regained in these animals and testing continued. Under test conditions, vehicle injections engendered no pregnanolone-appropriate responding. Pregnanolone engendered a dose-related increase in pregnanolone-appropriate responding with full substitution occurring at 5.6 and 10.0 mg/kg (Fig. 1). Partial substitution was observed at 3.0 and 1.0 mg/kg. Rates of responding after vehicle injections ranged from 1.28 to 4.35 responses/s with an average of 2.52 responses/s under the FR 10 schedule of reinforcement. Pregnanolone showed little effect on response rate at the doses tested.

The results from the generalization tests with the benzodiazepine receptor ligands are shown in Figs. 1 and 2. Triazolam (0.003–0.3 mg/kg, ip, 30 min, Fig. 1) completely substituted (> 80% pregnanolone-appropriate responding) in all rats tested at 0.1 and 0.3 mg/kg. The dose of 0.003 mg/kg showed no substitution and intermediate doses showed partial substitution. Similar to triazolam, lorazepam (0.1–3.0 mg/kg, ip, 30 min, Fig. 1) demonstrated dose-

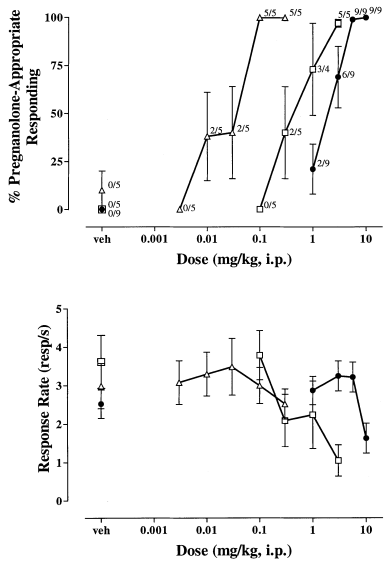

Fig. 1. Dose–response functions for pregnanolone (filled circles), triazolam (open triangles) and lorazepam (open squares) in rats trained to discriminate pregnanolone (5.6 or 8.0 mg/kg) from vehicle. Percentage pregnanolone-appropriate responding (upper panels) and response rate (responses/s; lower panels) are shown as a function of dose. Vehicle (veh) control values also are shown. Each point represents the mean of the data collected ($n = 9$ for pregnanolone, $n = 5$ for others). Vertical bars represent standard errors. The number of rats exhibiting substitution for the pregnanolone training dose/number of rats responding is given for each dose tested.

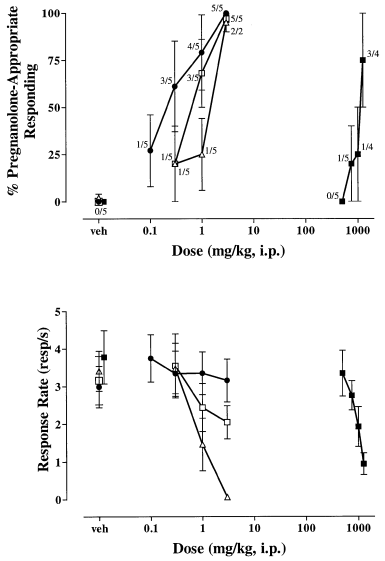

Fig. 2. Dose–response functions for bretazenil (filled circles), zolpidem (open triangles), zaleplon (open squares) and ethanol (filled squares) in rats trained to discriminate pregnanolone (5.6 or 8.0 mg/kg) from vehicle. Percentage pregnanolone-appropriate responding (upper panels) and response rate (responses/s; lower panels) are shown as a function of dose. Vehicle (veh) control values also are shown. Each point represents the mean of the data collected ($n=5$). Vertical bars represent standard errors. The number of rats exhibiting substitution for the pregnanolone training dose/number of rats responding is given for each dose tested.

related substitution with complete substitution for pregnanolone in all rats tested at 3.0 mg/kg. Partial substitution was engendered by intermediate doses and no substitution was engendered by the lowest dose tested (0.1 mg/kg). Unlike triazolam, lorazepam decreased response rate at the highest dose tested with responding at less than 50% of control rates.

Bretazenil (0.1–3.0 mg/kg, ip, 30 min; Fig. 2), the partial benzodiazepine receptor agonist, showed a dose-related increase in pregnanolone-appropriate responding with full substitution occurring at 3.0 mg/kg. Partial substitution occurred at all the other doses tested. Bretazenil had little effect on response rate.

The BZ1 selective agonist zolpidem (0.3–3.0 mg/kg, ip, 15 min; Fig. 2) completely substituted for pregnanolone at the highest dose of 3.0 mg/kg, but data for only two of five rats could be included due to the fact that the response rate of three rats was completely suppressed at this high dose. The two rats that did show substitution also exhibited very low response rates (12% and $<1\%$ of their own control rates). Lower doses of 0.3 and 1.0 mg/kg zolpidem showed full substitution in one rat and little or no substitution in the other rats, resulting in partial substitution with large variability. The intermediate dose of 1.0 mg/kg decreased response rate to less than 50% control rates, whereas the lowest dose tested had no effect on rate of responding.

The other BZ1 selective ligand tested, zaleplon (0.3–3.0 mg/kg, ip, 30 min; Fig. 2), substituted in all rats tested. The two higher doses showed full substitution, whereas the lowest dose showed partial substitution with large variability. Unlike zolpidem, zaleplon had little effect on response rate at the doses tested.

Ethanol (0.5–1.25 g/kg, ip, 30 min; Fig. 2) partially substituted for pregnanolone with only three of five rats exhibiting greater than 80% pregnanolone-appropriate responding at any dose. On the average, the lowest dose showed no substitution, whereas increasing doses caused a dose-related increase in pregnanolone-appropriate responding up to a maximum of 75% at the highest dose (1.25 g/kg). Ethanol reduced response rate at the highest dose with less than 50% control response rates.

4. Discussion

The present study confirms and extends a previous report that the neuroactive steroid pregnanolone could function as a discriminative stimulus [23]. Presently, the benzodiazepine agonists, triazolam and lorazepam, substituted for pregnanolone as a discriminative stimulus. These results are consistent with the substitution observed with diazepam for pregnanolone [23], and suggest shared discriminative stimulus effects of pregnanolone with benzodiazepines. However, the discriminative stimulus effects of neuroactive steroids and benzodiazepines are not identical. That lorazepam, but not triazolam, showed a concomitant decrease in response rate suggests that pregnanolone may be more similar to triazolam than it is to lorazepam. Similarly, allopregnanolone, another neuroactive steroid previously shown to substitute for pregnanolone as a discriminative stimulus [23], only substituted for diazepam at doses that also decreased response rate and failed to substitute for lorazepam [2]. Although allopregnanolone has not been trained as a discriminative stimulus, to the extent that allopregnanolone and pregnanolone are similar stimuli, the potential lack of cross-generalization between neuroactive steroids and lorazepam may be similar to that which has been previously reported between barbiturates and lorazepam [3–6].

In addition to the substitution of triazolam and lorazepam for pregnanolone, the present study showed complete substitution of bretazenil, zolpidem and zaleplon for pregnanolone. Previously, bretazenil has been shown to share discriminative stimulus effects with chlordiazepoxide [9,16], but curiously not with zolpidem [16] or zaleplon [24]. In the present experiment, there seemed to be some subtle differentiation between zolpidem and zaleplon, in that zolpidem greatly reduced rate of responding whereas zaleplon had little effect on response rate. Interestingly, in rats trained to discriminate zolpidem from saline, the drugs chlordiazepoxide, triazolam, lorazepam and zaleplon show dose-related increases in zolpidem-appropriate responding, but only at doses that reduce response rates [20,21]. The reduction in response rates may indicate decreased speci-

ficity of the discriminative stimulus effects. Further, lorazepam, triazolam and zaleplon fully substitute for chlordiazepoxide, whereas zolpidem only partially substitutes for chlordiazepoxide; all the drugs reduce response rates in chlordiazepoxide-trained rats [18,19]. Zaleplon, zolpidem and triazolam fully substitute for lorazepam, whereas chlordiazepoxide only partially substitutes for lorazepam [1,13]. Taken together, it appears that the discriminative stimulus effects of the BZ1 selective ligands zaleplon and zolpidem differ slightly from nonselective benzodiazepines and slightly from each other. Although the mechanism underlying the subtle differences between zaleplon and zolpidem remain unclear, the present results indicate that the discriminative stimulus effects of pregnanolone may be more similar to those of zaleplon than those of zolpidem.

Ethanol, a discriminative stimulus mediated by a variety of receptors including $GABA_A$, generalizes to allopregnanolone [12], chlordiazepoxide [11,22], lorazepam [17] and bretazenil [7], but only partially to zolpidem [7,17] and zaleplon [17]. Triazolam substitutes for ethanol, but only at a dose that significantly reduces rate of responding [22]. Conversely, when ethanol is tested for substitution in rats trained to discriminate $GABA_A$ positive modulators, asymmetrical generalization occurs. This is the case with chlordiazepoxide-trained animals that show only partial generalization to ethanol [11] and lorazepam trained as a discriminative stimulus fails to show any generalization to ethanol [6]. Similar results were observed in the present study in which ethanol exhibited only partial substitution for rats trained to discriminate pregnanolone from vehicle and only with a concomitant decrease in response rates.

Taken together, the results are consistent with the premise that $GABA_A$ receptors mediate the discriminative stimulus effects of pregnanolone. Although there is considerable overlap with the discriminative stimulus effects of the various $GABA_A$ positive modulators, subtle differences are evident. Pregnanolone appears to be more like triazolam, bretazenil and zaleplon and less like lorazepam, zolpidem and ethanol.

Acknowledgment

The author wishes to thank S. Robledo for excellent technical assistance.

References

[1] Ator NA. Drug discrimination: selectivity through multiple drug or dose training. Behav Pharmacol 1998;9(Suppl 1):S104.
[2] Ator NA, Grant KA, Purdy RH, Paul SM, Griffiths RR. Drug discrimination analysis of endogenous neuroactive steroids in rats. Eur J Pharmacol 1993;241:237–43.
[3] Ator NA, Griffiths RR. Lorazepam and pentobarbital drug discrimination in baboons: cross-drug generalization and interaction with Ro 15-1788. J Pharmacol Exp Ther 1983;226:776–82.
[4] Ator NA, Griffiths RR. Asymmetrical cross-generalization in drug discrimination with lorazepam and pentobarbital training conditions. Drug Dev Res 1989a;16:355–64.
[5] Ator NA, Griffiths RR. Differential generalization to pentobarbital in rats trained to discriminate lorazepam, chlordiazepoxide, diazepam, or triazolam. Psychopharmacology 1989b;98:20–30.
[6] Ator NA, Griffiths RR. Selectivity in the generalization profile in baboons trained to discriminate lorazepam: benzodiazepines, barbiturates and other sedative/anxiolytics. J Pharmacol Exp Ther 1997; 282:1442–57.
[7] Bienkowski P, Iwinska K, Stefanski R, Kostowski W. Discriminative stimulus properties of ethanol in the rat: differential effects of selective and nonselective benzodiazepine receptor agonists. Pharmacol Biochem Behav 1997;58:969–73.
[8] Bienkowski P, Kostowski W. Discriminative stimulus properties of ethanol in the rat: effects of neurosteroids and picrotoxin. Brain Res 1997;753:348–52.
[9] Bronson M, Chen H-C. Time course of discriminative stimulus effects of bretazenil and chlordiazepoxide in rats. Eur J Pharmacol 1996; 305:7–12.
[10] Deutsch SI, Mastropaolo J. Discriminative stimulus properties of midazolam are shared by a GABA-receptor positive steroid. Pharmacol Biochem Behav 1993;46:963–5.
[11] De Vry J, Slangen JL. Effects of training dose on discrimination and cross-generalization of chlordiazepoxide, pentobarbital and ethanol in the rat. Psychopharmacology 1986;88:341–5.
[12] Grant KA, Azarov A, Bowen CA, Mirkis S, Purdy RH. Ethanol-like discriminative stimulus effects of the neurosteroid 3α-hydroxy-5α-pregnan-20-one in female *Macaca fascicularis* monkeys. Psychopharmacology 1996;124:340–6.
[13] Griffiths RR, Sannerud CA, Ator NA, Brady JV. Zolpidem behavioral pharmacology in baboons: self-injection, discrimination, tolerance and withdrawal. J Pharmacol Exp Ther 1992;260:1199–208.
[14] Mintzer MZ, Frey JM, Griffiths RR. Zolpidem is differentiated from triazolam in humans using a three-response drug discrimination procedure. Behav Pharmacol 1998;9:545–59.
[15] Rowlett JK, Winger G, Carter RB, Wood PL, Woods JH, Woolverton WL. Reinforcing and discriminative stimulus effects of the neuroactive steroids pregnanolone and Co 8-7071 in rhesus monkeys. Psychopharmacology 1999;145:205–12.
[16] Sanger DJ. Further investigation of the stimulus properties of chlordiazepoxide and zolpidem. Agonism and antagonism by two novel benzodiazepines. Psychopharmacology 1987;93:365–8.
[17] Sanger DJ. The effects of new hypnotic drugs in rats trained to discriminate ethanol. Behav Pharmacol 1997;8:287–92.
[18] Sanger DJ, Benavides J. Discriminative stimulus effects of ω (BZ) receptor ligands: correlation with in vivo inhibition of [^{3}H]-flumazenil binding in different regions of the rat central nervous system. Psychopharmacology 1993;111:315–22.
[19] Sanger DJ, Morel E, Perrault G. Comparison of the pharmacological profiles of the hypnotic drugs, zaleplon and zolpidem. Eur J Pharmacol 1996;313:35–42.
[20] Sanger DJ, Perrault G, Morel E, Joly D, Zivkovic B. The behavioral profile of zolpidem, a novel hypnotic drug of imidazopyridine structure. Physiol Behav 1987;41:235–40.
[21] Sanger DJ, Zivkovic B. The discriminative stimulus properties of zolpidem, a novel imidazopyridine hypnotic. Psychopharmacology 1986;89:317–22.
[22] Sanger DJ, Zivkovic B. Discriminative stimulus effects of alpidem, a new imidazopyridine anxiolytic. Psychopharmacology 1994; 113:395–403.
[23] Vanover KE. Discriminative stimulus effects of the endogenous neuroactive steroid pregnanolone. Eur J Pharmacol 1997;327:97–101.
[24] Vanover KE, Barrett JE. Evaluation of the discriminative stimulus effects of the novel sedative-hypnotic CL 284,846. Psychopharmacology 1994;115:289–96.