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(±)-18-Methoxycoronaridine: A Novel *Iboga* Alkaloid Congener Having Potential Anti-Addictive Efficacy

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INTRODUCTION

(±)-18-Methoxycoronaridine [(±)-18-MC], originally synthesized by Martin Kuehne and Upul Bandarage at the University of Vermont, is a congener of ibogaine (Fig. 1), an alkaloid found in the root bark of the African shrub *Tabernanthe iboga*. In five United States patents (numbers 4,499,096; 4,587,243; 4,857,523; 5,026,697; 5,124,994) issued between 1985 and 1992, ibogaine has been claimed to be effective in treating opiate (heroin) addiction, stimulant (cocaine and amphetamine) abuse, alcohol dependence, cigarette smoking (nicotine dependence), and poly-drug abuse. Ibogaine supposedly interferes with the "physiological and psychological aspects" of addiction, abolishing the craving for drugs. According to the patents, a single treatment may be effective for six months and a series of four treatments may be effective for up to three years. Studies in animals have, to a limited extent, corroborated these claims. In rats ibogaine has been reported to decrease intravenous morphine (15) and cocaine (5,10) self-administration as well as oral intake of alcohol (36) and nicotine (12). Most of these effects last for a day or more after ibogaine treatment, well beyond the presence of the drug, or its metabolite noribogaine, in the brain (16,31).

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Fig. 1. Chemical structures of ibogaine and 18-methoxycoronaridine.

Reports of side effects of ibogaine have limited its therapeutic utility and seriously diminished the possibility of it ever receiving approval by the FDA. Aside from having stimulant and hallucinogenic properties, ibogaine induces tremors, manifested as whole body shaking in rats. The tremors are attributable to activation of an olivo-cerebellar pathway (cf. 27) and, in rats, occur in response to moderate doses (20–40 mg/kg) of ibogaine; the tremors are reduced after high doses (≥ 100 mg/kg) which, apparently by overstimulating cerebellar Purkinje cells (27–29), produce damage to the cerebellar vermis. Another side effect, a pronounced bradycardia, is not as well documented (7) but may have more clinical significance.

The problems associated with ibogaine led to attempts to develop a safer and still efficacious structural derivative. Initial work with other *iboga* alkaloids demonstrated that decreases in drug self-administration could be dissociated from tremorigenic activity: C-14R(–)-ibogamine and C-14R(–)-coronaridine (19), two non-tremorigenic iboga alkaloids, mimicked ibogaine's effects on morphine and cocaine self-administration (9). But, like ibogaine, these other alkaloids also had acute nonspecific effects, reducing responding for a non-drug reinforcer (water) as well as responding for drugs, during the first 1–2 h after administration. Several synthetic analogues of ibogamine and coronaridine had similar profiles of activity. However, (±)-18-MC was different: this non-tremorigenic iboga alkaloid congener mimicked ibogaine's effects on morphine and cocaine self-administration but had no acute depressant effect on responding for water. Further studies showed that (±)-18-MC also reduced alcohol and nicotine intake and produced no cerebellar toxicity. This report will review these studies as well as a variety of others aimed at characterizing both the *in vivo* and *in vitro* pharmacological actions of this compound.

CHEMISTRY

(±)-18-MC was obtained by a convergent synthesis (3) for which key steps are shown in Fig. 2. The compound, $C_{22}H_{28}N_2O_3$, mp 194–195°C, is soluble in ether, dichloromethane, ethanol, and dimethylsulfoxide. Its water soluble hydrochloride salt was used for all biological evaluations.

Fig. 2. Synthesis of racemic 18-methoxycoronaridine. Reagents and conditions: (a) toluene, reflux, 12 h, 96%; (b) NaBH4, HOAc, 90°, 5 min, 91%; (c) 10%Pd/C, H2, EtOAc/HOAc (10:1), 87%; (d) 10% HCl/MeOH, rt, 12 h, 76%; (e) toluene, reflux, 3 h, 70%.

PHARMACOLOGY

Drug Self-Administration Studies

(±)-18-MC was evaluated for its efficacy to influence the self-administration of four addictive drugs. The intravenous (i.v.) route was used to deliver morphine and cocaine. Female rats weighing approximately 250 g were trained to self-administer morphine (0.04 mg/kg/infusion) or cocaine (0.4 mg/kg/infusion) during daily one hour test sessions (9); each lever-press response produced either a 10 µl (morphine) or 50 µl (cocaine) infusion of drug solution (0.01 mg of morphine sulfate or 0.1 mg cocaine hydrochloride) in 0.1 (morphine) or 0.5 (cocaine) second. In order to provide an indication of the specificity of (±)-18-MC's effects on responding for morphine and cocaine, other rats trained to bar-press for water on a comparable schedule (continuous reinforcement; 1 h session) were also treated with (±)-18-MC. The effect of (±)-18-MC on nicotine self-administration was assessed in an oral model in which female rats had a choice of receiving either (–)-nicotine (4 ng/ml of the hydrogen bitartrate salt) by pressing one lever or water by pressing another lever in a two-lever operant chamber during daily 1-h test sessions (12). The effect of (±)-18-MC on alcohol intake was determined in male, selectively-bred alcohol-preferring rats. The animals were given a choice, (over 24 h) of drinking from one bottle containing a solution of 10% (v/v) ethanol or another bottle containing water (36).

Fig. 3. Dose-response effects of intraperitoneally administered (±)-18-MC on the self-administration of morphine, cocaine, nicotine, ethanol, and water (data derived from refs. 9, 9, 12, 36, and 9, respectively; see text for procedural details). There was no effect of (±)-18-MC on responding for water while doses of 20 and 40 mg/kg significantly decreased the intake of all the drugs. Each data point represents the mean (± SEM) of at least 6 rats.

In our initial studies, (±)-18-MC was administered by the intraperitoneal (i.p.) route. A dose-response comparison of the acute effects of i.p. (±)-18-MC on morphine, cocaine, alcohol and nicotine self-administration as well as on responding for water is shown in Fig. 3. (±)-18-MC reduced the self-administration of all four drugs to a similar extent but did not affect responding for water (9,12,36). At the highest dose (40 mg/kg), protracted effects were also observed: (±)-18-MC decreased morphine self-administration for at least two days after treatment, and cocaine and nicotine self-administration for at least one day; the same dose had no effect on responding for water while after-effects on alcohol intake were not assessed. In subsequent work, focusing on morphine self-administration, similar results were obtained when (±)-18-MC was administered orally (p.o.), via gavage (Fig. 4). Very high doses (80–160 mg/kg, p.o.) were also administered to rats responding for water: although such doses acutely depressed responding, complete recovery was apparent a day or more later. Thus, on the day of treatment, (±)-18-MC is relatively selective for drug (e.g., morphine) vs non-drug (water) responding, but in terms of its protracted effects, (±)-18-MC is totally selective.

The efficacy of (±)-18-MC on morphine self-administration seems to increase with repeated treatment. At 20 mg/kg, p.o., a single treatment with (±)-18-MC had no effect on morphine self-administration; however, by the fourth day of daily treatment, the same dose significantly decreased morphine intake (Fig. 5). Even five days of the same treatment had no effect on responding for water.

Although all of the preceding work was conducted with racemic 18-MC, we have recently assessed the effects of the (+) and (–) enantiomers of 18-MC on morphine self-administration. Administered p.o., at doses of 10–40 mg/kg, both enantiomers were active and their effects (reduced morphine self-administration at 40 mg/kg) were insignificantly different from each other as well as from the racemic compound.

Fig. 4. After-effects (mean ± SEM) of orally (gavage) administered (±)-18-MC (40 mg/kg) on intravenous morphine self-administration. (±)-18-MC was administered 30 min prior to testing on day 1; there were significant ($p < 0.05$) effects for at least two days afterwards.

Fig. 5. Effects (mean ± SEM) of repeated oral administration of (±)-18-MC (20 mg/kg) on morphine self-administration and on responding for water. (±)-18-MC had no effects on days 1–3 but significantly ($p < 0.05$) decreased morphine self-administration, without affecting responding for water, on days 4 and 5.

Drug craving, or "the desire to experience the effect(s) of a previously experienced psychoactive substance" (25), sustains and promotes addictive behavior. Craving is elicited by previously neutral stimuli that have become associated with the reinforcing effects of drugs. Several animal models of drug craving have been developed (cf. 25), and one of them, referred to as conditioned reinforcement, has been utilized in this laboratory to evaluate a potential anti-craving effect of (±)-18-MC. In the routine i.v. drug self-administration paradigm, a brief (0.5 second) pulse of light immediately precedes each drug in-

Fig. 6. Effects (mean ± SEM) of (±)-18-MC (40 mg/kg, p.o.) in conditioned reinforcement models of craving for cocaine and water. (±)-18-MC significantly ($p < 0.05$) decreased responding for the light (period 2) previously associated with cocaine but not for the light previously associated with water; (±)-18-MC also significantly ($p < 0.05$) increased the latency to respond for the cocaine-associated light but not for the water-associated light.

fusion. As a consequence of its association with the drug, the light becomes a secondary or conditioned reinforcer — and our craving paradigm makes use of this phenomenon.

After training rats to self-administer cocaine, rats were tested under one of two conditions. In one condition (extinction), the infusion pump and the associated light were simply turned off for the entire session. In the other condition (craving), the infusion pump was again turned off but the light was turned on for two seconds 20 min after the session started — for the next 20 min, each lever press turned the light on briefly but did not activate the infusion pump. During the last 20 min, both the infusion pump and the light were turned off, just as they were during the first 20 min. The same procedures were also conducted with other rats trained to respond for water (except that the water dipper was turned off instead of the infusion pump). The result was that, during the second 20 min, rats made approximately three times as many responses during the craving condition (light available) as in the extinction condition (light not available), and the effects were similar regardless of whether the previous reinforcer was cocaine or water. When administered to rats tested in the craving condition, (±)-18-MC (40 mg/kg, p.o.) decreased responding for the light only in rats previously trained with cocaine; rats previously trained to respond for water were unaffected (Fig. 6). Another measure of craving, the latency to make the first response after presentation of the light at the beginning of the second 20 min, was also measured: (±)-18-MC increased this latency in cocaine-trained rats but not in water-trained rats. Thus the data suggest that (±)-18-MC reduced "craving" for cocaine but not for water.

One last issue that was addressed in a self-administration experiment was the possibility that (±)-18-MC itself might be reinforcing. Rats were first trained to self-administer cocaine and then (±)-18-MC, at various concentrations (0.4–1.6 mg/kg/infusion), was

Fig. 7. Cumulative response records of an individual rat when self-administering cocaine, (±)-18-MC, or saline. Note the consistent pattern of responding for cocaine; in contrast, rats made bursts of responses, indicative of extinction, when (±)-18-MC or saline was substituted for cocaine.

substituted for cocaine. The temporal pattern of responding clearly indicated that (±)-18-MC was not reinforcing (Fig. 7); rats showed extinction patterns very similar to those occurring when saline was substituted for cocaine. Furthermore, when rats were allowed to self-administer (±)-18-MC for several days, responding progressively declined.

In Vivo Microdialysis Studies

It is now well established that the rewarding effects of many drugs of abuse are, to some extent, all mediated by the mesolimbic dopaminergic pathway originating in the ventral tegmental area and innervating the nucleus accumbens (NAC). Although through different mechanisms, opioids, stimulants, ethanol and nicotine all increase extracellular levels of dopamine in the NAC. Consistent with an anti-addictive action, (±)-18-MC (9), like ibogaine (22), was found acutely (within the first three hours of administration) to decrease dopamine release in the NAC. Other studies at longer posttreatment intervals showed that (±)-18-MC, like ibogaine, interfered with drug-induced increases in dopamine in the NAC. Thus (±)-18-MC pretreatment (19 hours beforehand), like ibogaine pretreatment (22, 23), blocked morphine-induced (Fig. 8) and nicotine-induced (12) do-

Fig. 8. Effects (mean ± SEM) of (±)-18-MC pretreatment (40 mg/kg, i.p., 19 h beforehand) on the maximal increase in extracellular dopamine levels in the nucleus accumbens elicited by morphine (5 mg/kg, i.p.), cocaine (20 mg/kg, i.p.) and nicotine (0.32 mg/kg, i.v.).

pamine release in the NAC. However, (±)-18-MC pretreatment had no effect on cocaine-induced increases in NAC dopamine whereas ibogaine pretreatment enhanced this action of cocaine (21). These results suggest that (±)-18-MC and ibogaine have somewhat different mechanisms of action and that different mechanisms underlie their behavioral interactions with opioid vs. stimulant drugs. Another distinction between (±)-18-MC and ibogaine is that whereas ibogaine as well as noribogaine increase extracellular levels of serotonin in the NAC, (±)-18-MC has no effect (42).

Further evidence of a complex mode of action of (±)-18-MC has come from a comparison of the 18-MC enantiomers. Although, as noted above, both enantiomers decreased morphine self-administration, only the (+) enantiomer decreased dopamine release in the NAC. This suggests that, with respect to dopamine terminals in the NAC, the (+) and (–) enantiomers may have pre- and post-synaptic actions, respectively, that equally contribute to the efficacy of the racemic compound.

In Vitro Studies

The results of an extensive receptor screen comparing the binding affinities of (±)-18-MC, (+)-18-MC, (–)-18-MC, ibogaine and noribogaine are shown in Table 1. Consistent with previous studies (4,6,18,20,30,32,34,39–41), ibogaine and noribogaine have low micromolar affinities for several sites, including kappa and mu opioid receptors, NMDA receptors, $5HT_3$ receptors, $sigma_2$ sites, sodium channels and the serotonin transporter; functional studies (2,38) have also shown ibogaine to behave as a noncompetitive antagonist at nicotinic receptors, acting perhaps as an open channel blocker that is not revealed in binding studies.

The binding profiles of the 18-MC's are somewhat different than that of ibogaine. (±)-18-MC has low micromolar affinities at all three opioid receptors and at $5HT_3$ re-

TABLE 1. Interactions of (±)-18-MC, (+)-18-MC, (–)-18-MC, ibogaine, and noribogaine with the target sites listed below (values are μM K_i)

Parameter	Ligand	Tissue	(±)-18-MC	(+)-18-MC	(–)-18-MC	Ibogaine	Noribogaine
Kappa opioid	[^{3}H]-U69593	Calf cortex	5.1 ± 0.50	4.8 ± 0.35	5.5 ± 0.61	2.2 ± 0.10	0.61 ± 0.015
Mu opioid	[^{3}H]-DAGO	Calf cortex	1.1 ± 0.30	0.74 ± 0.07	13 ± 0.09	2.0 ± 0.15	0.68 ± 0.016
Delta opioid	[^{3}H]-DPDPE	Calf caudate	3.5 ± 0.05	3.8 ± 0.10	>100	>10	5.2 ± 0.64
Nociceptin	[^{3}H]-nociceptin	Bovine cortex	>100	>100	>100	>100	>100
NMDA	[^{3}H]-MK801	Bovine cortex	>100	>100	>100	3.1 ± 0.30	15 ± 2.0
D_1	[^{3}H]-SCH23390	Calf caudate	>100	>100	>100	>10	>10
D_2	[^{3}H]-N-methyl-spiperone	Calf caudate	16 ± 0.60	>100	11 ± 0.40	>10	>10
D_3	[^{3}H]-7-OH-DPAT	Calf caudate	25 ± 2.5	>100	16 ± 0.58	70 ± 1.7	>100
M_1	[^{3}H]-pirenzepine	Calf cortex	32 ± 3	30 ± 3.3	>100	16 ± 1.0	15 ± 1.0
M_2	[^{3}H]-QNB	Calf cortex	>100	>100	>100	31 ± 3.4	36 ± 3.7
5-HT_{1A}	[^{3}H]-8-OH-DPAT	Rat hippocampus	46 ± 4.9	>100	>100	>100	>100
5-HT_{1B}	[^{3}H]-serotonin	Calf caudate	>100	>100	>100	>100	>100
5-HT_{1C}	[^{3}H]-mesulergine	Calf cortex	>100	>100	>100	>100	>100
5-HT_{1D}	[^{3}H]-serotonin	Calf caudate	>10	>100	>100	>100	>100
5-HT_{2A}	[^{3}H]-ketanserin	Gf-6 cells	40 ± 3.4	>100	>100	16	>100
5-HT_{2C}	[^{3}H]-mesulergine	J-1 cells	>100	>100	>100	>10	>10
5-HT_3	[^{3}H]-GR-65,630	NG-108 cells	3.8 ± 0.067	2.2 ± 0.23	>100	2.6 ± 0.23	>100
Sodium channel	[^{3}H]-BTX-B	Bovine cortex	6.4 ± 0.68	7.3 ± 0.67	8.5 ± 0.03	3.6 ± 0.35	17 ± 0.6
$Sigma_1$	[^{3}H]-(+)-pentazocine	Calf caudate	>100	>100	>100	2.5 ± 0.6	11 ± 1.7
$Sigma_2$	[^{3}H]-DTG	Calf hippocampus	13 ± 1.2	11 ± 1.2	11 ± 1.1	0.4 ± 0.036	19 ± 1.3
$GABA_B$	[^{3}H]-GABA	Calf cortex	>100	>100	>100	>100	>100
NE uptake	[^{3}H]-nisoxetine	Bovine cortex	>10	>10	3.9 ± 0.12	>100	39 ± 1.5
5-HT uptake	[^{3}H]-paroxetine	Bovine brain stem	>10	>10	>10	4.1 ± 0.83	0.57 ± 0.083

ceptors but no affinity at NMDA receptors or the serotonin transporter. While the affinities of (+)-18-MC and (–)-18-MC at the kappa opioid receptor are equivalent, the (+) enantiomer has more than a tenfold higher affinity than the (–) enantiomer at mu and delta opioid receptors. Affinities of the enantiomers are comparable at sodium channels and at $sigma_2$ sites while (+)-18-MC is more potent at the M_1 muscarinic site and (–)-18-MC is more potent at dopamine D_2 receptors and at the norepinephrine transporter. All of these affinities are in the low micromolar range and it is difficult to envision how any of these actions could be responsible for "therapeutic" effects lasting 24–48 h. However, some of these actions may be relevant to acute side effects and be responsible for a potentially higher therapeutic index of (±)-18-MC relative to ibogaine. Actions of ibogaine at muscarinic (M_1 and M_2) receptors and at sodium channels may be responsible for its cardiovascular toxicity (bradycardia); and ibogaine's affinity is 2–3 times greater than that of 18-MC (racemic as well as enantiomers) at all of these sites. Ibogaine's action at $sigma_2$ sites has been related to its neurotoxicity (41), and its $sigma_2$ affinity is approximately thirty-fold greater than that of the 18-MC's. We have previously proposed that the hallucinogenic effect of ibogaine is attributable to serotonin release, an effect not exhibited by (±)-18-MC (42). Lastly, it should be noted that preliminary data in this laboratory suggest that (±)-18-MC, like ibogaine, may have a nanomolar affinity for nicotinic channels — and such an action might indeed account for prolonged therapeutic effects.

PHARMACOKINETICS AND TOXICITY

Plasma Half-Life and Tissue Distribution

We have used gas chromatography-mass spectrometry (GCMS) to develop a quantitative method for measuring (±)-18-MC in plasma and tissues. Analysis of plasma levels after i.v. administration of (±)-18-MC indicates that (±)-18-MC has a short initial half-life (about 5–10 min); however, the data do not fit a one-compartment model and, using a two-compartment model, which does fit the data, there is a terminal half-life of over 100 min (Fig. 9).

Analysis of tissue levels after i.p. and p.o. administration (Fig. 10) shows that (±)-18-MC is highly sequestered in fat; at four hour after administration, levels in fat are approximately 30 times as high as levels in plasma or brain. The sequestration in fat is consistent with the elimination data fitting a two-compartment model and with the fact that the calculated volume of distribution of (±)-18-MC is very large (4–6 L in rats). It should be noted, however, that, in absolute terms, even fat levels of (±)-18-MC are low and that the total amount of (±)-18-MC measured in tissues accounts for only a small fraction (less than 10%) of the administered dose. This suggests that (±)-18-MC is rapidly metabolized, probably subject to a very substantial first-pass effect. The deposition in fat could account for (±)-18-MC's prolonged duration of action (i.e., fat being a natural depot) providing that (±)-18-MC has a much greater affinity for a site of action that we have not yet identified (i.e., micromolar potency at opioid receptors is not consistent with the low tissue levels). Alternatively, (±)-18-MC might have an active and very potent me-

Fig. 9. Time course of disappearance of (±)-18-MC (mean ± SEM) from plasma following i.v. infusion. Rats chronically implanted with i.v. and intra-arterial cannulas received (±)-18-MC hydrochloride (40 mg/kg, i.v., 10 mg/ml) infused at 30 µl/min over 30 min. Arterial samples were collected at the times shown (zero representing the end of the infusion). The curve shows fits to bi-exponential (solid line) and mono-exponential (dashed line) decay functions.

Fig. 10. Distribution of (±)-18-MC (mean ± SEM) in rat plasma, brain and fat four hours after i.p. and p.o. administration (40 mg/kg).

tabolite, such that the drug deposited in fat serves as a long-term depot of precursor for conversion to the active moiety.

Assessment of Potential Neurotoxicity

Ibogaine induces whole body tremors at moderates doses (20–40 mg/kg) and degeneration of cerebellar Purkinje cells at high doses (≥ 100 mg/kg) (27–29). It was, therefore,

important to consider the possibility that these effects would also occur in response to (±)-18-MC. Visual observations and videotape recordings of (±)-18-MC-treated (40 mg/kg) rats indicated very little if any tremorigenic activity; (±)-18-MC could not be distinguished from saline (27). Similarly, even multiple, high doses (100 mg/kg) of (±)-18-MC failed to produce degeneration of Purkinje cells above that normally seen in the cerebellum, consistent with its low affinity for $sigma_2$ sites (Table 1 and ref. 41).

At 40 mg/kg, the most effective dose in the drug self-administration studies, (±)-18-MC-treated rats appear entirely normal. Confirming this, Fig. 11 shows that (±)-18-MC, 40 mg/kg, does not alter locomotor activity for at least three h after administration.

Cardiovascular Effects

Anecdotal reports suggest that ibogaine slows the heart rate in humans. In preliminary studies ($N = 2–3$/dose) in this laboratory with awake and freely moving rats, implanted with femoral artery catheters, ibogaine produced no changes in heart rate or blood pressure at 40 mg/kg but, at 100 and 200 mg/kg, it progressively decreased heart rate without altering blood pressure. (±)-18-MC, at 200 mg/kg, had no apparent effects on either heart rate or blood pressure. Fig. 12 shows typical results with 200 mg/kg of ibogaine and (±)-18-MC.

DISCUSSION AND CONCLUSIONS

Based on the results from various animal models, (±)-18-MC would appear to share all of ibogaine's putative anti-addictive effects but lack ibogaine's potential to produce neurological and cardiovascular toxicity. (±)-18-MC's acute effects are also more selective than ibogaine's in that drug self-administration can be reduced without altering responding for a non-drug reinforcer (water). The issue of how (±)-18-MC, as well as ibogaine, alters sensitivity to self-administered drugs is not entirely settled. That is, at least for morphine (9,15), neither (±)-18-MC nor ibogaine appears to simply shift the dose-response curve for the self-administered drug to the left or to the right. Earlier results with ibogaine (24) and recent preliminary results with (±)-18-MC indicate that both agents produce a downward shift in the morphine dose-response curve. The fact that ibogaine and (±)-18-MC reduce the maximal response to morphine suggests that they effectively lower what has been referred to as the "hedonic set point" (1). Phrased anthropomorphically, we would expect that, under the influence of (±)-18-MC or ibogaine, people would experience less of a "high" in response to an opioid drug.

The mechanism of action of (±)-18-MC is still largely unknown. Other data indicating that μ antagonists (17), δ antagonists (33), and κ agonists (11) modulate cocaine as well as morphine self-administration suggest that (±)-18-MC's affinities for all three opioid receptors may be important; however, the fact that all of these affinities are in the

Fig. 11. Locomotor activity (photocell counts; mean ± SEM) of rats for three hours after administration of (±)-18-MC (40 mg/kg, i.p.) or saline. There was no significant effect of (±)-18-MC.

Fig. 12. Individual effects of 200 mg/kg (p.o.) of (±)-18-MC and ibogaine on systolic and diastolic blood pressure and on heart rate in awake and freely moving rats. Note the substantial decrease in heart rate produced by ibogaine but not by (±)-18-MC (first ↑ = vehicle; second ↑ = drug).

micromolar range is hard to reconcile with the fact that (±)-18-MC is behaviorally effective when plasma and brain levels are very low. Furthermore, other functional effects of (±)-18-MC are inconsistent with it being either an agonist or an antagonist at μ receptors; thus (±)-18-MC (37), like ibogaine (8,14), attenuates naltrexone-precipitated withdrawal symptoms in morphine dependent rats (i.e., inconsistent with it being a μ antagonist) and, in preliminary studies, has very little or no analgesic efficacy (i.e., inconsistent with it being a μ agonist). (±)-18-MC's short half-life suggests that at least part of its pharmacology is attributable to one or more active metabolites. The deposition of (±)-18-MC in fat, and perhaps of active metabolites as well, may result in a slow release of active compounds mediating (±)-18-MC's prolonged effects.

Lastly, until clinical trials are initiated, it will not be known whether (±)-18-MC shares ibogaine's hallucinogenic property. However, unlike ibogaine, (±)-18-MC does not raise extracellular levels of serotonin (42). To the extent that the serotonergic actions of ibogaine are important in this regard, we would predict that (±)-18-MC will lack hallucinogenic activity.

In conclusion, (±)-18-MC is a novel *iboga* alkaloid congener that has the potential to become a safe and effective treatment for multiple forms of drug abuse. Further investigation of its mode of action should be instrumental in elucidating the neurobiology of drug addiction and in providing a rational basis for designing new agents with improved efficacy.

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