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SUPPRESSION OF MORPHINE AND COCAINE SELF-ADMINISTRATION IN RATS BY A MIXED MU ANTAGONIST-KAPPA AGONIST (N-CBM-TAMO) AND A LONG-ACTING SELECTIVE D_1 ANTAGONIST (AS-300)

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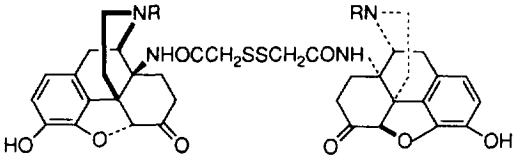
Abstract: N-CBM-TAMO **2** was prepared by the same procedure as used for TAMO **1.** It was found to be a short-term kappa agonist and a long-term mu antagonist. The benzazepine **12,** (AS-300) was a potent selective D_1 antagonist. Both compounds suppressed cocaine and morphine self-administration in rats at doses which did not affect water consumption.

Mu opioid antagonists increase and kappa opioid agonists decrease dopamine (DA) release in the nucleus accumbens (NA) of freely moving rats.[1] Jaffe and Martin[2] cited evidence that microinjection of mu agonists into the ventral tegmental area activate dopaminergic neurons that project into the NA.



1, R = CH_3 (TAMO)

2, R = CH_2-◇ (N-CBM-TAMO)

We have shown by microdialysis experiments that the kappa agonist, U50488, prevents the increase in DA caused by administration of cocaine and that U50488 and spiradoline reduce the self-administration of cocaine and morphine in rats.[3,4]

We have prepared an analog of TAMO **1**, the N-cyclobutylmethyl compound **2**, by a procedure previously employed for the preparation of **TAMO**[5] and in binding assays in bovine striatal membranes[6] displayed the following affinities: mu, IC_{50} (nM±S.E) vs 0.25nM [^{3}H]DAMGO =1.95 ± 0.22; delta, vs 0.2nM [^{3}H]p-ClDPDPE = 11.9 ± .5: kappa, vs 1 nM [^{3}H]U69,593 = 6.29 ± .97.

In the warm water tail-flick assay in mice, ligand **2** was a partial agonist. A maximum of a 70% effect was reached after a dose of 100 nmol given icv. In the mouse writhing test the D_{50}

value was 0.08 nmol after icv administration. Both TAMO **1** and N-CBM-TAMO **2** were long-term μ antagonists (data not shown) but **2** was a potent short term κ agonist whereas **1** was a short-term μ agonist.[6]

Since μ antagonists and κ agonists prevent the release of DA caused by administration of cocaine and morphine the effect of N-CBM-TAMO was studied in rats trained to self-administer these drugs. The dose-response curves are shown in Figure 1.

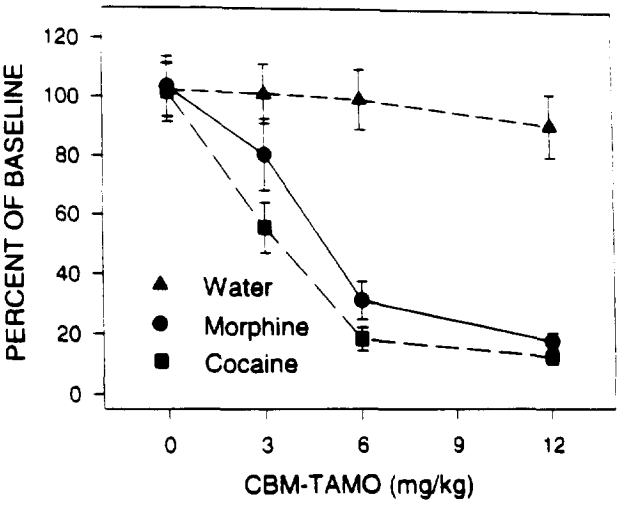


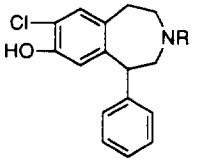
Figure 1. Dose response curves for the effect of N-CBM-TAMO 2 on the self-administration of morphine cocaine and water.

A dose of 12 mg/kg (ip) of **2** suppressed cocaine and morphine self-administration for two to three days. Recovery was complete in six days. At no time was the intake of water suppressed at this dose level. Thus it seems that compounds that are both κ agonists and μ antagonists produce satisfactory inhibition of self-administration of cocaine and morphine in rats without affecting consumption of water.

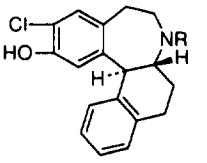
Presumably, DA released by cocaine and morphine will bind to a dopamine receptor in the nucleus accumbens. Thus a centrally-acting dopamine antagonist should also prevent or reduce self-administration of cocaine and morphine.

SCH 23390 **3** is a relatively short-acting, selective D_1 antagonist,[7] whereas SCH39166 **4** is somewhat longer acting[8]. Baindur et al [9] prepared some N-allyl analogs of SCH23390 but in all cases reported the ligands were less potent than the N-methyl analog. In an attempt to prepare

long-acting D_1 antagonists, Cross and his colleagues[10] synthesized the N-chloroethyl analog **5**, a maneuver that resulted in a severe loss of binding affinity.



3, SCH23390, R = CH_3
5, R = CH_2CH_2Cl



4, SCH39166

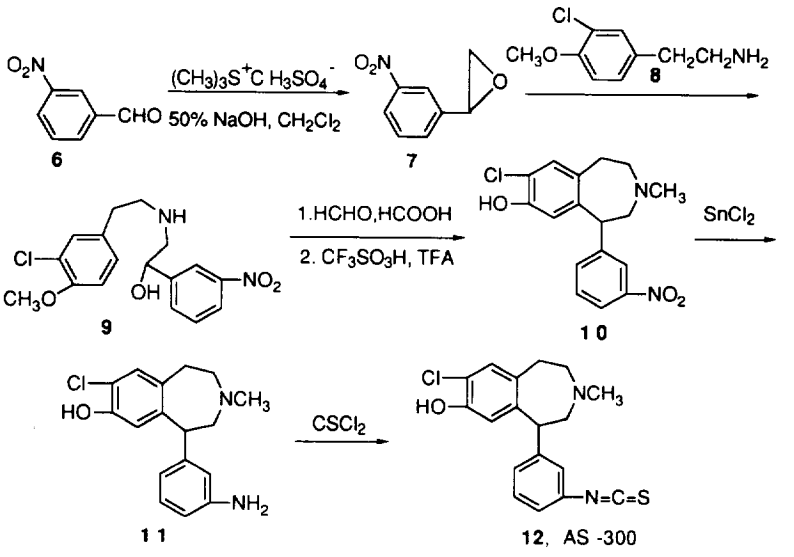
Recently, Shah et al.[11] prepared several other N-substituted analogs of **3** but these were also less potent than **3**.

Bergman and his colleagues[12] found that certain D_1 antagonists reduce the rate of bar-pressing in monkeys dependent on cocaine and Caine et al.[13] reported that SCH23390 produced rapid effects on cocaine self-administration when injected into the amygdala or the NA. Shippenberg and Herz[14] found that SCH23390 produced conditioned place aversions in rats given morphine and Nakajima and Wise[15] reported that an ip injection of SCH23390 suppressed bar-pressing in rats reinforced with an iv . heroin infusion. Gerrits et al.[16] claimed that the reduction in the initiation of heroin self-administration caused by the injection of SCH23390 into the NA was due to the effect of the drug on motor behavior rather than to blockade of the D_1 receptors. From a preponderance of the evidence cited above it seems reasonable to believe that the preparation and biological evaluation of a long-acting, selective D_1 antagonist would be worthwhile. To the best of our knowledge such a ligand has not yet been prepared. In view of the experience of others,[10,11] manipulation of the nitrogen substituent would not appear to be a profitable approach. The introduction of a functional group that would permit irreversible binding to the D_1 receptor could be accomplished by introducing an isothiocyanate group on the unsubstituted phenyl ring of SCH23390. The use of SCH23390 as a scaffold would ensure that the ligand would be a D_1 antagonist and the isothiocyanate group would furnish covalent binding as well as antagonist activity. To this end compound **12** was synthesized as shown in Scheme 1.

m-Nitrobenzaldehyde **6** was converted to the epoxide **7** using the method of Mosset and Gree.[17] The rest of the procedure was a slight modification of that described by Chumpradit and

co-workers[18] who used this synthesis to prepare (±)-7-chloro-8-hydroxy-1--(4')-[^{125}I]iodophenyl)-3-methyl-1,2,3,4-tetrahydro-1*H*-3-benzazepine via the intermediacy of the

SCHEME 1



corresponding 4'-bromo compound. N-Methylationof **9** followed by treatment with trifluoromethane sulfonic acid rather than sulfuric acid[18] gave the benzazepine **10.** Reduction with $SnCl_2$ gave the amine **11** which upon reaction with thiophosgene furnished the target compound **12** (AS-300).

D_1 and D_2 binding assays were carried out as described previously.[19] The results were as follows: D_1 IC_{50} vs 1 nM [^{3}H]SCH23390 = 2.13 nM and D_2 IC_{50} vs 10 nM [^{3}H]N-methylspiperone = 978 nM. Wash experiments revealed that AS-300 did not wash out of the preparation after four washes. Thus AS-300 behaves as a non-equilibrium ligand which binds selectively to the D_1 receptor with high affinity. The drug was administered to rats previously treated with amphetamine, and **12** reduced the increase in locomotor activity caused by the stimulant The close structural resemblance of AS-300 to the D_1 antagonist SCH23390, the fact that AS-300 was a non-equilbrium ligand and the ability of the drug to antagonize the locomotor stimulant effects of amphetamine support the conclusion tha AS-300 is a D_1 antagonist. AS-300 was administered at a dose of 1 mg/kg (ip) to rats trained to self-administer cocaine and morphine.

The self-administration of both cocaine and morphine was markedly suppressed. At this dose there was no interference with water intake. (Figure 2) Te drug did not interfere with motor behavior as reported by the van Ree group for SCH23390.[16]

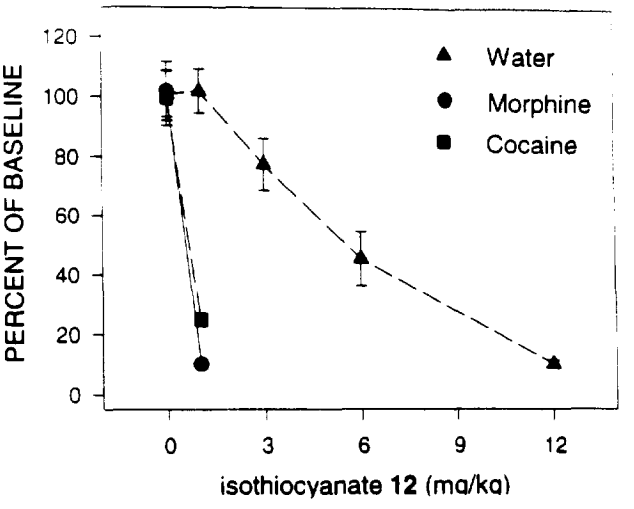


Figure 2. Dose response curves for the effect of AS-300 12 on the self-administration of morphine, cocaine and water.

The depression of cocaine and morphine intake lasted for about one to two days. The fact that self-administration of cocaine and morphine was suppressed at a dose that did not interfere with water intake suggests that a selective, long-acting D_1 antagonist may be a potentially novel treatment for opioid and stimulant addiction.

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