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Effects of Catecholamine-Related Mammalian Alkaloids on Spontaneous and Vasopressin-Induced Behavior in Mice

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MEISENBERG, G., W. H. SIMMONS AND M. A. COLLINS. *Effects of catecholamine-related mammalian alkaloids on spontaneous and vasopressin-induced behavior in mice.* PHARMACOL BIOCHEM BEHAV **20**(3) 355–360, 1984.— Heterocyclic catechol derivatives (tetrahydroisoquinoline alkaloids) are known to be formed endogenously *via* condensation of the catecholamines with carbonyl compounds. In this study, the effects of a variety of representative simple isoquinolines, benzyl isoquinolines, bicyclic isoquinoline-derived alkaloids (pavines and isopavines), an aporphine and berberine were investigated after intracerebroventricular injection in mice. Most (thirteen) of the alkaloids studied were found to induce significant alterations in three behavioral parameters (immobility, grooming and scratching behavior). In addition, the stereotypic scratching behavior elicited by central injection of arginine-vasopressin (AVP) was significantly antagonized by only one of these, 6-O-methyl-tetrahydropapaveroline (6-O-methyl-THP). To a lesser extent, (-)THP and the pavine, (±)bisnorargemonine, were also effective. That this rather specific alkaloid effect did not involve opioid receptors was indicated by the failure of naloxone to reverse the antagonism by 6-O-methyl-THP.

Vasopressin Mammalian alkaloids Catecholamines Tetrahydroisoquinolines Naloxone

IN addition to the well-established enzymatic routes of catecholamine (CA) metabolism such as deamination, O-methylation and (glucoronide or sulfate) conjugation, there is accumulating evidence for non-enzymatic reactions (condensations) of CAs with aldehydes or alpha-keto-acids. Various stable CA condensation products, tetrahydroisoquinoline (TIQ) alkaloid in structure, now have been detected and measured in mammalian tissues [2,14]. Increased formation of certain of these "mammalian alkaloids" may occur as a result of the altered metabolic states associated with alcoholism [4,21] or phenylketonuria [10].

Although alkaloids of mammalian importance have not been systematically examined for their behavioral effects in rodents and primates, some provocative data are available [14]. With selected alkaloids, central administration afforded dopamine agonist-like responses; in other studies, certain alkaloids induced behavioral supersensitivity characteristic of neuroleptics. Analgesic effects that might indicate interaction of TIQ alkaloids with endogenous opioid receptors is suggested by some experiments with opiate antagonists [7], but this is not supported by in vitro studies with guinea pig ileum [17]. Central TIQ administration in rats [15] and monkeys [16] was reported to induce an ethanol preference which was blocked by naloxone or naltrexone. Also of interest is the report that salsolinol, a condensation product of dopamine (DA) and acetaldehyde, antagonized the arginine-vasopressin (AVP)-induced contractions of the guinea pig sacculus [8].

In the present study, a systematic investigation of mammalian (TIQ-related) alkaloids was done using two simple behavioral screening tests after intracerebroventricular (ICV) injection in mice. Among these alkaloids are the bicyclic pavines and isopavines, which in theory could result from internal cyclization of a norepinephrine (NE)-derived tetrahydropapaveroline (THP)-like alkaloid [19], analogous to plant biogenesis pathways. The effects were compared with those of a DA receptor agonist, a delta-opiate receptor agonist, and a mu-opiate receptor agonist. Also, the reversibility of any "opiate-like" behavioral effects by naloxone was examined in order to determine if the effects were due to a direct action on endorphin receptors or to an opioid-peptide releasing action.

METHOD

The five simple DA- or DOPA-derived catecholic and phenolic TIQs, and the benzyl TIQ, THP, all shown in Fig. 1, were synthesized in pure form in our laboratories by condensation reactions described in detail elsewhere [2]. Purities were assessed by high performance liquid chroma-

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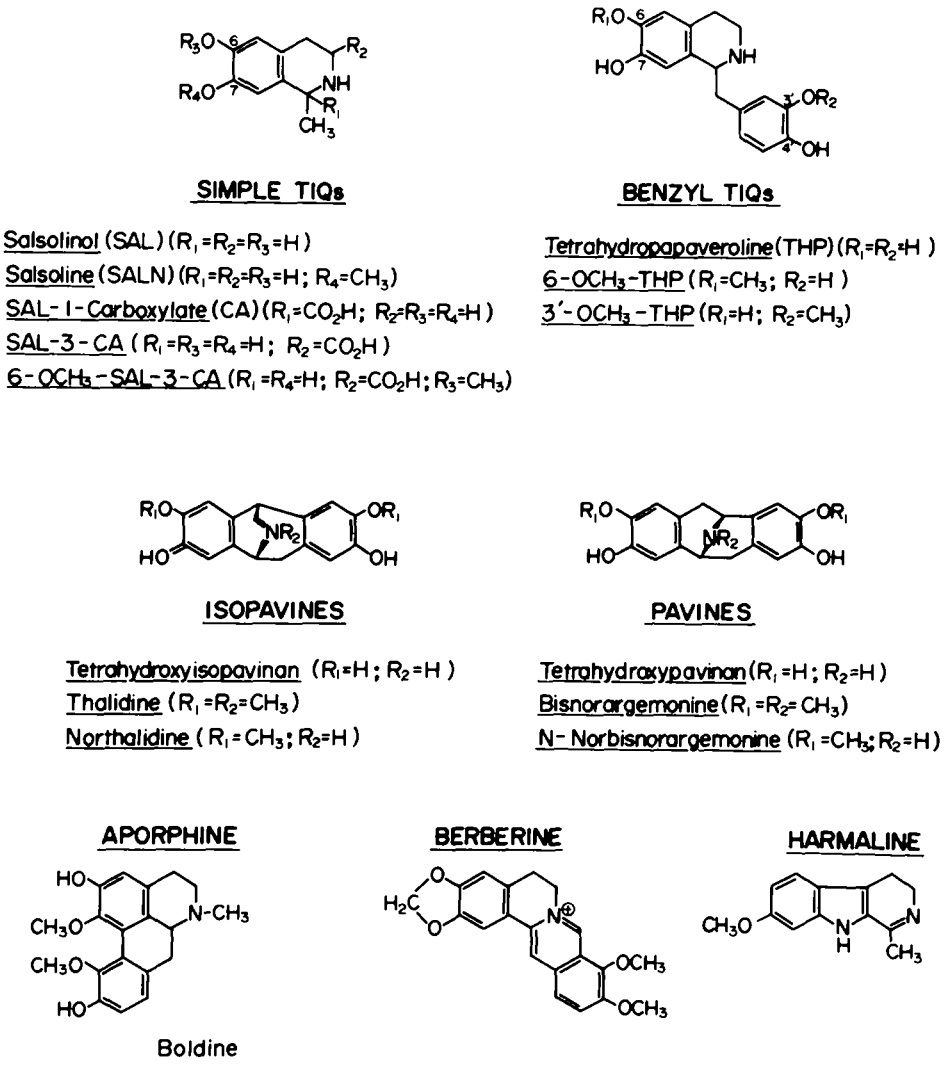

FIG. 1. Structures of alkaloids examined in this study.

tography [2, 3, 20]. Structures were proven by infra-red and nuclear magnetic resonance spectroscopy and melting point comparisons with the literature. The two O-methyl-THP isomers and the six pavines and isopavines in Fig. 1 were gifts from Dr. Arnold Brossi of NIMH. Boldine, berberine, harmaline, apomorphine, morphiceptin and D-Ala^2-D-Leu^5-enkephalin (DADL) were purchased from Sigma Chemical Co. 8-Arginine-vasopressin (AVP) was sythesized at the University of Illinois Medical Center in the laboratory of the late Roderich Walter.

Male Swiss-Webster mice, 25–35 g, were used. The animals were housed at 24° in a 12 hr light/12 hr dark cycle in groups of 5 per cage, with food and water available ad lib. The compounds were dissolved immediately before use in artificial CSF solution consisting of 128 mM NaCl, 3.0 mM KCl, 1.0 mM $MgCl_2$, 1.25 mM $CaCl_2$ and 1 mM glucose in 10 mM NaOAc buffer, pH 5. A slightly acidic pH was used to minimize oxidation of the alkaloids. Mice were injected over a period of 30 seconds ICV under light ethyl ether anesthesia with a Hamilton microsyringe at a site 1–2 mm lateral from the midline. An injection volume of 20 μl, which had previously been found to be optimal for the induction of behavioral excitation after ICV injection of vasopressin [12], was used in all experiments. Control injections of a 1% solution of methylene blue showed that this procedure resulted in a distribution of the injected solution throughout the ventricular system. In previous studies [12,13], no irreversible behavioral alterations were found after this injection procedure, even if the mice were injected repeatedly. This suggests that tissue damage is not involved in the induction of behavioral alterations after ICV injection.

Injected mice were placed individually in a 16.5×26.5 cm transparent cage and in the timed period between 5 and 10 minutes after the injection, immobility, grooming and scratching were determined cumulatively in seconds/test session for the whole 5-minute period. Using this timing,

TABLE 1

EFFECTS OF ISOQUINOLINE-RELATED ALKALOIDS ON SPONTANEOUS BEHAVIOR IN MICE*

Treatment	(Dose)	(Sec/Session ± S.D.) Immobility	Grooming	Scratching
CSF	—	94.5 ± 19.6	49.6 ± 10.7	1.0 ± 0.3
Apomorphine	(10 μg)	209.0 ± 25.8‡	9.9 ± 4.7§	0.0§
Apomorphine	(25 μg)	56.8 ± 33.1	1.5 ± 0.7§	0.1 ± 0.1‡
Morphiceptin	(5 μg)	152.5 ± 30.5	0.9 ± 0.7§	0.1 ± 0.1‡
Morphiceptin	(20 μg)	162.2 ± 43.3	13.5 ± 11.1‡	0.1 ± 0.3
DADL†	(50 ng)	51.0 ± 20.8	19.7 ± 6.4‡	1.5 ± 1.1
DADL	(250 ng)	293.0 ± 7.0§	0.0§	0.0§
Serotonin	(10 μg)	91.0 ± 39.9	51.7 ± 25.6	0.7 ± 0.7
Serotonin	(25 μg)	249.3 ± 28.8§	0.0§	0.0§
Harmaline	(50 μg)	262.2 ± 11.0§	5.8 ± 4.9§	0.0§
Simple TIQs				
(+) SAL	(50 μg)	152.2 ± 51.5	27.8 ± 20.9	1.0 ± 0.7
(−) SALN	(50 μg)	264.7 ± 10.5§	1.6 ± 1.4§	0.0§
(±) SAL-1-CA	(50 μg)	138.0 ± 23.7	34.5 ± 16.6	0.3 ± 0.3
(±) SAL-3-CA	(50 μg)	65.5 ± 27.8	44.5 ± 11.7	1.7 ± 0.8
(±) 6-OCH_3-SAL-3-CA	(50 μg)	97.8 ± 33.5	43.3 ± 18.3	0.0§
Benzyl TIQs				
(±) THP	(10 μg)	100.8 ± 22.2	23.0 ± 15.5	0.0§
(−) THP	(50 μg)	191.4 ± 27.9§	4.6 ± 2.9§	0.0§
(+) THP	(50 μg)	50.2 ± 36.2	16.2 ± 5.4§	1.5 ± 1.5
(±) 6-OCH_3-THP	(10 μg)	102.0 ± 27.3	33.6 ± 10.0	1.1 ± 0.4
(±) 6-OCH_3-THP	(50 μg)	188.0 ± 32.6‡	16.4 ± 7.1‡	0.5 ± 0.5
(−) 3′-OCH_3-THP	(50 μg)	239.8 ± 23.6§	5.5 ± 2.9§	0.0§
Other Alkaloids				
Boldine	(10 μg)	174.0 ± 50.2	22.0 ± 14.2	1.0 ± 0.6
Boldine	(50 μg)	253.7 ± 12.1§	5.3 ± 3.8§	0.0§
Berberine	(10 μg)	149.8 ± 35.1	28.0 ± 16.3	0.5 ± 0.3
Berberine	(50 μg)	234.7 ± 12.0§	9.7 ± 4.7§	0.0§

N=6 to 20 mice per group. All values are determined cumulatively; Seconds per 5-minute test-session.
†DADL = D-Ala^2-Leu^5-enkephalin.
‡ = $p < 0.05$.
§ = $p < 0.01$; Student t-test, compared with CSF.

interference by the other anesthesia is minimized while the metabolically labile alkaloids and vasopressin are still active. The alkaloids were injected either alone or in combination with 5 ng AVP. As shown previously, this dose of AVP reduces immobility and markedly increases grooming and particularly scratching [12]. The observation that both amphetamines and an opioid peptide block AVP-induced scratching behavior led to the suggestion that this test may be useful as a primary screening device for psychotropic drugs, particularly those activating DA systems or those acting on opiate receptors [13].

RESULTS

In Table 1 are the effects on spontaneous activity of the mammalian alkaloids, excluding the pavines and isopavines, and for comparison, the effects of some other compounds with known neuropharmacological activities. An increase in immobility, accompanied by decreased grooming activity, was observed with several of the alkaloids, including SALN, (−)THP, (±)6-O-methyl-THP, (±)3′-O-methyl-THP, boldine and berberine. Similar effects, however, were induced by apomorphine, the opioid peptides morphiceptin and DADL, serotonin, and the beta-carboline, harmaline. When studied in combination with AVP (Table 2), the only alkaloids in Table 1 to significantly antagonize AVP-induced scratching behavior were (±)6-O-methyl-THP and, with lower potency, (−)THP.

The effects of the pavine and isopavine alkaloids are shown in Table 3. All of these compounds, which exhibit a high degree of structural rigidity, proved to be quite active in the behavioral test. At the higher dose (50 μg), toxic effects were evident, although no deaths occurred; specifically, (±)N-norbisnorargemonine, (±)tetrahydroxyisopavinan, (±) tetrahydroxypavinan and (±)N-northalidine caused disturbances of motor co-ordination, and convulsions were occasionally seen after the last two alkaloids. Although it did not show overt signs of toxicity, the pavine, (±) bisnorargemonine, was the only alkaloid in this table to effec-

TABLE 2

EFFECTS OF ISOQUINOLINE-RELATED ALKALOIDS ON VASOPRESSIN(AVP)-INDUCED BEHAVIOR IN MICE*

Treatment	(Dose)	(Sec/Session ± S.D.) Immobility	Grooming	Scratching
CSF	—	94.5 ± 19.6	49.6 ± 10.7	1.0 ± 0.3
AVP	(5 ng)	19.6 ± 9.4	107.6 ± 9.6	69.5 ± 7.5
AVP + Apomorphine	(10 μg)	120.1 ± 22.7§	41.4 ± 10.8§	21.6 ± 8.0§
AVP + Apomorphine	(25 μg)	121.8 ± 17.8§	3.9 ± 2.6§	0.5 ± 0.4§
AVP + Morphiceptin	(5 μg)	130.0 ± 37.8§	15.6 ± 8.9§	20.4 ± 11.8§
AVP + Morphiceptin	(20 μg)	174.8 ± 26.7§	0.7 ± 0.7§	0.0§
AVP + DADL†	(50 ng)	251.3 ± 12.8§	0.0§	1.0 ± 0.6§
AVP + DADL	(250 ng)	86.1 ± 31.9‡	7.0 ± 4.0§	0.1 ± 0.1§
AVP + Serotonin	(10 μg)	13.1 ± 7.1	77.1 ± 17.8	23.9 ± 5.8§
AVP + Serotonin	(25 μg)	232.2 ± 46.1§	0.0	0.7 ± 0.7§
AVP + Harmaline	(50 μg)	82.1 ± 30.1‡	31.0 ± 18.1§	103.0 ± 22.9
Simple TIQs				
AVP + SAL	(50 μg)	128.5 ± 30.7§	19.4 ± 9.0§	23.3 ± 22.3‡
AVP + SALN	(50 μg)	213.0 ± 32.2§	1.3 ± 0.9§	67.1 ± 30.3
AVP + SAL-1-CA	(50 μg)	73.5 ± 36.0	87.3 ± 30.9	40.5 ± 19.7
AVP + SAL-3-CA	(50 μg)	39.3 ± 18.5	68.0 ± 16.0‡	53.0 ± 23.9
AVP + 6-OCH_3-SAL-3-CA	(50 μg)	46.0 ± 26.9	48.2 ± 16.6§	59.3 ± 26.2
Benzyl TIQs				
AVP + (−)THP	(10 μg)	4.5 ± 3.3	124.0 ± 29.9	42.0 ± 8.2
AVP + (−)THP	(50 μg)	200.4 ± 34.6§	27.5 ± 14.2§	25.0 ± 16.4‡
AVP + (+)THP	(50 μg)	50.6 ± 28.5	75.8 ± 13.0‡	76.0 ± 18.0
AVP + 6-OCH_3-THP	(10 μg)	138.6 ± 26.4§	26.0 ± 12.5§	1.4 ± 0.5§
AVP + 6-OCH_3-THP	(50 μg)	181.3 ± 32.5§	16.0 ± 5.6§	3.5 ± 2.1§
AVP + 3'-OCH_3-THP	(50 μg)	51.2 ± 17.3	70.5 ± 21.6	52.3 ± 20.1
AVP + Boldine	(10 μg)	3.1 ± 2.1	98.3 ± 15.9	61.6 ± 8.8
AVP + Berberine	(10 μg)	0.8 ± 0.5‡	88.8 ± 14.9	61.8 ± 14.9

*N = 6 to 20 mice per group. Alkaloids were injected along with AVP in a single ICV injection. Results are seconds per 5-minute test-session.

†DADL = D-Ala^2-Leu^5-enkephalin.

‡ = $p < 0.05$.

§ = $p < 0.01$; Student t-test. Compared with AVP.

tively antagonize AVP-induced scratching in a manner similar to (±)6-O-methyl-THP and (−)THP.

Naloxone reversibility of the morphiceptin or DADL antagonism of AVP-elicited stereotypic behavior is demonstrated in Table 4. However, as shown, the opiate receptor antagonist failed to reverse the blocking effects of 6-O-methyl-THP or bisnorargemonine on AVP-induced behavior.

DISCUSSION

With the exception of the two carboxylated SALs, all of the TIQs tested in this study caused statistically significant behavioral alterations, either alone or in combination with vasopressin. This shows that "mammalian alkaloids" are not biologically inert CA products, and may be relevant physiologically or pathophysiologically if produced in sufficient quantities and at specific loci in vivo. To date, SAL and SALN [18, 21, 22] have been detected in brain, and THP is formed after L-DOPA treatment [20,23].

In terms of mechanisms of action, the effects of 6-O-methyl-THP and (±)bisnorargemonine on vasopressin-induced behavior, although phenotypically very similar to those of DADL and morphiceptin, clearly are not due to a direct action on delta or mu opiate receptors, or to the release of endogenous endorphins, as evidenced by the failure of naloxone to block the effects of these alkaloids. We cannot exclude the possibility, however, that release or potentiation of endogenous opioids at selected brain sites mediates some of the effects of TIQs on spontaneous behavior. The reported ability of THP to act on opiate receptors in vitro at very high doses [7] is unlikely to be relevant at the doses used in this study. Other mechanisms might involve DA receptors [1,24], or possibly the serotonergic system, since several TIQ alkaloids are known to alter brain serotonin levels following administration [5, 9, 11].

The fairly high behavioral toxicity of the catecholic and phenolic pavines and isopavines suggests that these unusual alkaloids, if they are formed endogenously in adrenergic neurons from 4-hydroxylated THP precursors [19], could be of pathophysiological relevance, for instance, in the context of alcoholism or of degenerative nervous system diseases.

TABLE 3

PAVINES AND ISOPAVINES: EFFECTS ON SPONTANEOUS AND VASOPRESSIN(AVP)-INDUCED BEHAVIOR IN MICE*

Alkaloid	(Dose)	(Sec/Session ± S.D.) Immobility	Grooming	Scratching
CSF	(—)	44.8 ± 18.6	44.5 ± 12.2	0.4 ± 0.4
AVP	(5 ng)	27.4 ± 12.8	105.4 ± 12.3	65.9 ± 9.6
(+) Bisnorargemonine	(50 μg)	196.8 ± 26.2‡	5.0 ± 2.0‡	0.7 ± 0.4
AVP + (±) Bisnorargemonine	(50 μg)	83.5 ± 30.8‡	17.5 ± 3.9‡	4.6 ± 2.5‡
(±)-N-Norbisnorargemonine	(10 μg)	52.7 ± 42.6	23.7 ± 10.7	0.0
(±)-N-Norbisnorargemonine	(50 μg)	228.2 ± 6.0‡	1.5 ± 1.5‡	0.0
(±)-2,3,8,9-Tetrahydroxy-isopavinan	(10 μg)	18.3 ± 12.4†	7.5 ± 3.6‡	1.3 ± 0.8
(±)-2,3,8,9-Tetrahydroxy-isopavinan	(50 μg)	163.0 ± 53.8	0.0‡	2.2 ± 2.2
AVP + (±)-2,3,8,9-Tetrahydroxy-isopavinan	(10 μg)	0.0*	48.6 ± 18.3†	115.6 ± 19.5†
(+)-N-Northalidine	(10 μg)	280.5 ± 7.3‡	0.8 ± 0.8‡	0.0
(+)-N-Northalidine	(50 μg)	294.2 ± 3.6‡	0.0‡	0.0
AVP + (±)-N-Northalidine	(10 μg)	189.8 ± 21.6‡	4.9 ± 1.9‡	33.2 ± 7.0‡
(±)-2,3,8,9-Tetrahydroxy-pavinan	(10 μg)	0.0	0.4 ± 0.4‡	0.0
(+)--2,3,8,9-Tetrahydroxy-pavinan	(50 μg)	1.5 ± 1.5‡	0.0‡	0.0
AVP + (±)-2,3,8,9-Tetrahydroxy-pavinan	(10 μg)	5.5 ± 10.4†	61.7 ± 10.4†	69.8 ± 28.0

*N = mice per group. Results are given in seconds per 5-minute test-session.
†=$p<0.05$.
‡=$p<0.01$; Student t-test. Compared with CSF or AVP respectively.

TABLE 4

INTERACTIONS OF 6-OCH_3-THP AND (±)-BISNORARGEMONINE WITH VASOPRESSIN (AVP) IN NALOXONE-TREATED MICE*

Pretreatment†	Treatment	(Dose)	(Sec/Session ± S.D.) Immobility	Grooming	Scratching
NaCl	AVP	(5 ng)	2.9 ± 2.0	73.6 ± 11.8	107.3 ± 14.0
NaCl	Morphiceptin	(20 μg) +AVP	175.8 ± 35.1	10.3 ± 4.5	0.3 ± 0.2
Naloxone	Morphiceptin	(20 μg) + AVP	0.3 ± 0.3	65.7 ± 29.5‡	49.3 ± 13.4‡
NaCl	DADL	(50 ng) + AVP	152.0 ± 43.2	13.5 ± 7.2	2.7 ± 2.1
Naloxone	DADL	(50 ng) + AVP	1.3 ± 1.3‡	81.1 ± 14.8‡	55.9 ± 11.7‡
NaCl	6-OCH_3-THP	(10 μg) + AVP	174.8 ± 28.7	23.8 ± 12.5	2.5 ± 2.1
Naloxone	6-OCH_3-THP	(10 μg) + AVP	167.4 ± 30.8	15.9 ± 9.6	0.4 ± 0.3
NaCl	(±) Bisnorargemonine	(50 μg) + AVP	212.0 ± 18.1	4.1 ± 1.0	4.9 ± 0.3
Naloxone	(±) Bisnorargemonine	(50 μg) + AVP	181.4 ± 26.9	3.0 ± x1.0	9.2 ± 5.6

*N = 6 to 10 mice per group. Results are seconds per 5-minute test-session.
†Intraperitoneal injection of NaCl or 10 mg/kg Naloxone 30 minutes before the test.
‡$p<0.01$, student t-test. Compared with NaCl-pretreated controls.
DADL = D-Ala-Leu-enkephalin.

The several unidentified catecholic "alkaloidal" substances separated from incubations of labelled NE with brain or liver homogenates [6] might consist of bicyclic pavines or isopavines rather than or in addition to the suggested benzyl THP. Clearly, more information about the possible formation of these compounds is required.

Particularly novel and interesting is the rather specific antagonism of the stereotypic response of centrally-administered AVP by 6-O-methylated THP and to a lesser degree, by its bicyclic analogue (bisnorargemonine). Other O-methyl isomers of THP, including the stereoisomers of reticuline (6,4'-di-O-methyl-N-methyl-THP) and nor-

reticuline, will be examined to obtain a more complete structure/activity relationship. While the present study provides a survey of the behavioral effects of isoquinoline-based mammalian alkaloids, the biochemical mechanisms and sites of action have to be investigated in more detail.

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